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(71) Applicant (for all designated States except US): LIGAND PHARMACEUTICALS INCORPORATED [US/US]; 10275 Science Center Drive, San Diego, CA 92121-1117 (US).

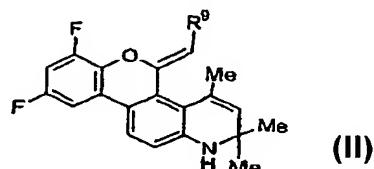
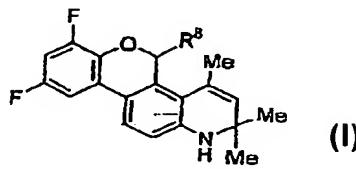
(72) Inventors; and

(75) Inventors/Applicants (for US only): ZHI, Lin [CN/US]; 3988 Via Cangrejo, San Diego, CA 92130 (US). VAN EVEREN, Cornelis, Arjan [NL/US]; 3635 Promontory Place, Carlsbad, CA 92008 (US). PEDRAM, Bijan [CA/US]; 7665 Palmilla Drive, Apt. #5103, San Diego, CA 92122 (US). KARANEWSKY, Donald [US/US]; 1797 Continental Lane, Escondido, CA 92029 (US).



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(54) Title: 5-SUBSTITUTED 7,9-DIFLUORO-5H-CHROMENO[3,4-f]QUINOLINE COMPOUNDS AS SELECTIVE PROGESTERONE RECEPTOR MODULATORS



(57) Abstract: The present invention is directed to compounds of formula (I) or (II), pharmaceutical compositions, and methods for modulating processes mediated by progesterone receptor. Also provided are methods of making such compounds and pharmaceutical compositions.

5-SUBSTITUTED 7,9-DIFLUORO-5H-CHROMENO[3,4-f]QUINOLINE
COMPOUNDS AS SELECTIVE PROGESTERONE RECEPTOR MODULATORS

Field of the Invention

5 This invention relates to 5-substituted 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline compounds that may be highly potent receptor- and tissue-selective modulators (*i.e.* agonists, partial agonists and antagonists) of progesterone receptors and to methods for the making and use of such compounds.

Background of the Invention

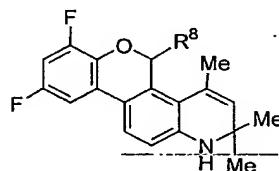
10 Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroid PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins as female birth control agents or hormone
15 replacement therapies must be weighed against the increased risk of breast cancer due to progestins' proliferative activity in breast tissue. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a glucocorticoid receptor
20 (GR) antagonist. Accordingly, identification of compounds that have good receptor-selectivity for PR over other steroid hormone receptors as well as good tissue-selectivity (*e.g.* selectivity for uterine tissue over breast tissue) would be of significant value in the improvement of women's health.

A group of nonsteroidal molecules which contain a di- or tetra-hydroquinoline ring as core pharmacophore (Todd, Jones; *et al.* US Patent Nos. 5,693,646; 5,693,647 and 5,696,127) (M.J. Coghlan *et al.*, PCT Publication Nos. WO 99/41256 A1 and WO 99/41257 A1) have been described as steroid hormone receptor modulator compounds.

The entire disclosures of the publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

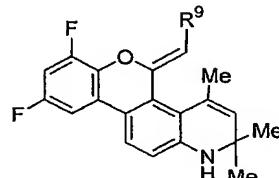
Summary of the Invention

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. More particularly, the invention relates to 5-substituted 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline compounds and compositions which may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and/or antagonists for progesterone receptors. Also provided are methods of making such compounds and pharmaceutical compositions. Compounds of the present invention may be represented by the formulae:



(1)

or



2

(II)

wherein:

R^8 is selected from the group of C_1 – C_{12} alkyl, C_1 – C_{12} heteroalkyl, C_1 – C_{12} haloalkyl, C_2 – C_{12} alkenyl, C_2 – C_{12} heteroalkenyl, C_2 – C_{12} haloalkenyl, C_2 – C_{12} alkynyl,
 5 C_2 – C_{12} heteroalkynyl, C_2 – C_{12} haloalkynyl, aryl and heteroaryl, wherein said alkyl, heteroalkyl, haloalkyl, alkenyl, heteroalkenyl, haloalkenyl, heteroalkynyl, haloalkynyl, alkynyl, aryl and heteroaryl groups are optionally substituted;

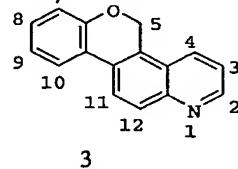
R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1 – C_8 alkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, C_2 – C_8 alkenyl, C_2 – C_8 heteroalkenyl, C_2 – C_8 haloalkenyl,
 10 C_2 – C_8 alkynyl, C_2 – C_8 heteroalkynyl, C_2 – C_8 haloalkynyl, aryl and heteroaryl, wherein said alkyl, heteroalkyl, haloalkyl, alkenyl, heteroalkenyl, haloalkenyl, heteroalkynyl, haloalkynyl, alkynyl, aryl and heteroaryl groups are optionally substituted;

and pharmaceutically acceptable salts and prodrugs thereof.

Definitions and Nomenclature

15 As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

20 A 5*H*-chromeno[3,4-*f*]quinoline is defined by the following structure.



The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain or cyclic alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,3-butadienyl and the like.

Allyl alone or in combination refers to $-\text{CH}_2\text{CH=CH}_2$.

15 Methylidene alone or in combination refers to $=\text{CH}_2$.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain-alkyl radicals having one or more carbon-carbon triple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl" refers to alkyl groups, as described above, in which one or more skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof. The term heteroalkyl also includes alkyl groups in which 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms 5 are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polycyclic rings and polycyclic aromatic ring systems containing from six to about twenty carbon 10 atoms. The term aryl also includes monocyclic aromatic rings, polycyclic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polycyclic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

15 The term "heteroaryl" refers to an optionally substituted aromatic ring system containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term 20 heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (e.g., a six

membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, 5 purinyl, indolizinyl, thienyl and the like.

The terms haloalkyl, haloalkenyl, haloalkynyl and haloalkoxy include alkyl, alkenyl, and alkynyl structures, as described above, that are substituted with one or more fluorines, chlorines, bromines or iodines, or with combinations thereof.

The terms cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl 10 and heteroalkyl include optionally substituted cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl groups.

The term "carbocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which all of the skeletal atoms are carbon.

The term "heterocycle" includes optionally substituted, saturated or unsaturated, 15 three- to eight-membered cyclic structures in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

The term "acyl" includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound via a carbonyl functionality (e.g., -CO-alkyl, -CO- 15 aryl, -CO-arylalkyl or -CO-heteroarylalkyl, etc.).

20 The term "halogen" includes F, Cl, Br and I.

The term "mediate" means affect or influence. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a

role. Progesterone receptors are known to play a role in conditions including, for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood disorder, osteoporosis, and hormone-dependent cancers.

5 The term “receptor-selectivity” refers to compounds that display modulating activity towards a particular receptor (e.g., a progesterone receptor) without displaying substantial cross-reactivity towards another receptor (e.g., glucocorticoid receptor). Thus, for example, selective compounds of the present invention may display modulating activity towards progesterone receptors without displaying substantial cross-reactivity 10 towards other steroid hormone receptors.

15 The term “tissue-selectivity” refers to compounds that display full modulating activity in one tissue (e.g., uterine tissue) while displaying partial modulating activity in other tissue (e.g., breast tissue). Thus, for example, tissue-selective compounds of the present invention may display full modulating activity in uterine and vaginal tissues with partial modulating activity (partial agonistic or partial antagonistic) in breast tissues 15 relative to the full activities of the marketed steroidal progestins in all of the target tissues.

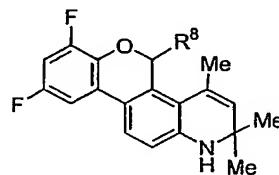
The term “modulate” means affect or influence. Thus, compounds that “modulate” a receptor affect the activity, either positively or negatively, of that receptor.

20 The term may be used to refer to the activity of compounds of a receptor as, for example, an agonist, partial agonist or antagonist. The term also may be used to refer to the effect that a compound has on a physical and/or physiological condition of an individual. For example, certain compounds of the present invention may be used to modulate fertility in an individual. That is, certain compounds of this invention may be used to increase the

fertility of an individual, while other compounds of this invention may be used to decrease the fertility of an individual.

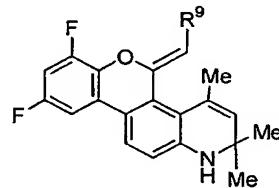
Detailed Description of the Invention

Compounds of the present invention may be represented by the formulae:



(I)

or



(II)

10 wherein:

R⁸ is selected from the group of C₁–C₁₂ alkyl, C₁–C₁₂ heteroalkyl, C₁–C₁₂ haloalkyl, C₂–C₁₂ alkenyl, C₂–C₁₂ heteroalkenyl, C₂–C₁₂ haloalkenyl, C₂–C₁₂ alkynyl, C₂–C₁₂ heteroalkynyl, C₂–C₁₂ haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

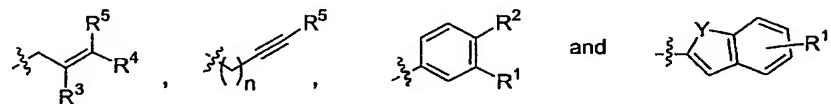
15 R⁹ is selected from the group of hydrogen, F, Cl, Br, I, CN, C₁–C₈ alkyl, C₁–C₈ heteroalkyl, C₁–C₈ haloalkyl, C₂–C₈ alkenyl or cycloalkenyl, C₂–C₈ heteroalkenyl, C₂–C₈ haloalkenyl, C₂–C₈ alkynyl, C₂–C₈ heteroalkynyl, C₂–C₈ haloalkynyl, aryl and heteroaryl 20 optionally substituted with one or more substituents independently selected from the

group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹; and

R¹⁰ and R¹¹ each independently is hydrogen or C₁–C₄ alkyl; and

5 pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment, R⁸ is selected from the group of:



R¹ and R² each independently is selected from the group of hydrogen, F, Cl, Br and C₁–C₄ alkyl;

10 R³ through R⁵ each independently is selected from the group of hydrogen, F, Cl and C₁–C₄ alkyl;

R⁶ is selected from the group of hydrogen, F, Cl, Br, C₁–C₄ alkyl, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

R⁷ is hydrogen, F, or Cl;

15 R¹⁰ and R¹¹ each independently is hydrogen or C₁–C₄ alkyl;

n is 0 or 1;

X is CH or N; and

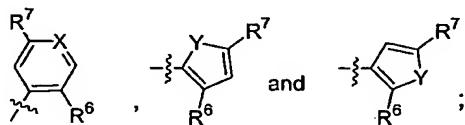
Y is selected from the group of O, S, and NR¹⁰;

and pharmaceutically acceptable salts and prodrugs thereof.

In another embodiment, R^6 is selected from the group of F, Me, Et, OMe, OEt, SMe, and NMe₂.

In another embodiment, R^9 is selected from the group of:

5



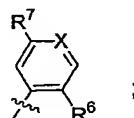
R^6 is selected from the group of hydrogen, F, Cl, Br, C₁–C₄ alkyl, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

X is CH or N; and

R^7 is hydrogen, F, or Cl; and

10 Y is selected from the group of O, S, and NR¹⁰.

In another embodiment, R^9 is



R^6 is selected from the group of hydrogen, F, Cl, Br, C₁–C₄ alkyl, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

15 R^7 is hydrogen, F, or Cl; and

X is CH or N.

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a progesterone receptor modulator compound of formulae I or II shown above wherein R¹ through R¹¹, n, X, Y, have the same definitions as given above.

5 In a further aspect, the present invention comprises a method of modulating a process mediated by progesterone receptors comprising administering to a patient having a condition mediated by progesterone receptors an effective amount of a compound of the formulae I or II shown above, wherein R¹ through R¹¹, n, X, Y, have the same definitions as those given above.

10 Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, 15 stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

20 PR agonist, partial agonist and antagonist compounds of the present invention may be particularly useful for female hormone replacement therapy and as modulators of fertility (e.g., as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen receptor modulators. PR modulator compounds of this invention also may be

used in the treatment of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. The PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, 5 endometrium and prostate. PR modulator compounds of this invention can also be used in treatment of female osteoporosis, either alone or in combination with one or more estrogen receptor modulators.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as selective agonists, partial agonists or 10 antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (*i.e.*, progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activities, may prove useful. Specifically, the mixed MR 15 effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that occur.

Furthermore, it will be understood by those skilled in the art that compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to 20 treat the conditions and diseases described above. Thus, compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative PR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:

7,9-difluoro-5(*Z*)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 10);

5 7,9-difluoro-5(*Z*)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 12);

7,9-difluoro-5(*Z*)-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 13);

10 7,9-difluoro-5(*Z*)-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 14);

7,9-difluoro-5(*Z*)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 15);

7,9-difluoro-5(*Z*)-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 16);

15 7,9-difluoro-5(*Z*)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 17);

7,9-difluoro-5(*Z*)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 18);

20 7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 19);

7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 20);

7,9-difluoro-5(*Z*)-(2-methyl-3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 21);

5 7,9-difluoro-5(*Z*)-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 22);

7,9-difluoro-5(*Z*)-(2,3-dimethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 23);

10 7,9-difluoro-5(*Z*)-cyanomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 24);

7,9-difluoro-5(*Z*)-hexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 25);

7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 26);

15 7,9-difluoro-5(*Z*)-(2,4,5-trifluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 27);

7,9-difluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 28);

20 7,9-difluoro-5(*Z*)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 29);

7,9-difluoro-5(*Z*)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 30);

7,9-difluoro-5(*Z*)-(2-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 31);

5 (±)-7,9-difluoro-5-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 32);

(±)-7,9-difluoro-5-phenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 33);

10 (±)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 34);

(±)-7,9-difluoro-5-(1,3-benzodioxol-5-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 35);

(±)-7,9-difluoro-5-(4-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 36);

15 (±)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 37);

(-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 38);

20 (+)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 39);

(\pm)-7,9-difluoro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 40);

(\pm)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 41);

5 (\pm)-7,9-difluoro-5-(3-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 42);

(\pm)-7,9-difluoro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 43);

10 (\pm)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 44);

(\pm)-7,9-difluoro-5-(2-oxo-2-phenylethyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 45);

(\pm)-7,9-difluoro-5-ethyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 46);

15 (\pm)-7,9-difluoro-5-ethenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 47);

(\pm)-7,9-difluoro-5-(2-oxo-3-butenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 48);

20 Methyl (\pm)-7,9-difluoro-1,2-dihydro- $\alpha,\alpha,2,2,4$ -pentamethyl-5*H*-chromeno[3,4-*f*]quinoline-5-ethanoate (Compound 49);

(\pm)-7,9-difluoro-5-ethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 50);

(\pm)-7,9-difluoro-5-cyano-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 51);

5 (\pm)-7,9-difluoro-5-butyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 52);

(\pm)-7,9-difluoro-5-(2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 53);

10 (\pm)-7,9-difluoro-5-(2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 54);

(\pm)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 55);

(\pm)-7,9-difluoro-5-[3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 56);

15 Ethyl (\pm)-7,9-difluoro-1,2-dihydro- α -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanoate (Compound 57);

_____ (\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol (Compound 58);

20 (\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol acetate(Compound 59);

(\pm)-7,9-difluoro-5-(1-methylethethyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 60);

(\pm)-7,9-difluoro-5-(N-methyl-2-pyrrolyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 61);

5 (\pm)-7,9-difluoro-5-phenylethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 62);

(\pm)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 63);

10 (-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 64);

(+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 65);

(\pm)-7,9-difluoro-5-(5-methyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 66);

15 (\pm)-7,9-difluoro-5-(2-benzo[b]furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 67);

(\pm)-7,9-difluoro-5-[4-(dimethylamino)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 68);

(\pm)-7,9-difluoro-5-(5-methyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 69);

(\pm)-7,9-difluoro-5-(5-methoxy-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 70);

(\pm)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 71);

5 (-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 72);

(+)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 73);

10 (\pm)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 74);

(-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 75);

(+)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 76);

15 (\pm)-7,9-difluoro-5-(4,5-dimethyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 77);

(\pm)-7,9-difluoro-5-(2-methyl-1-propenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 78);

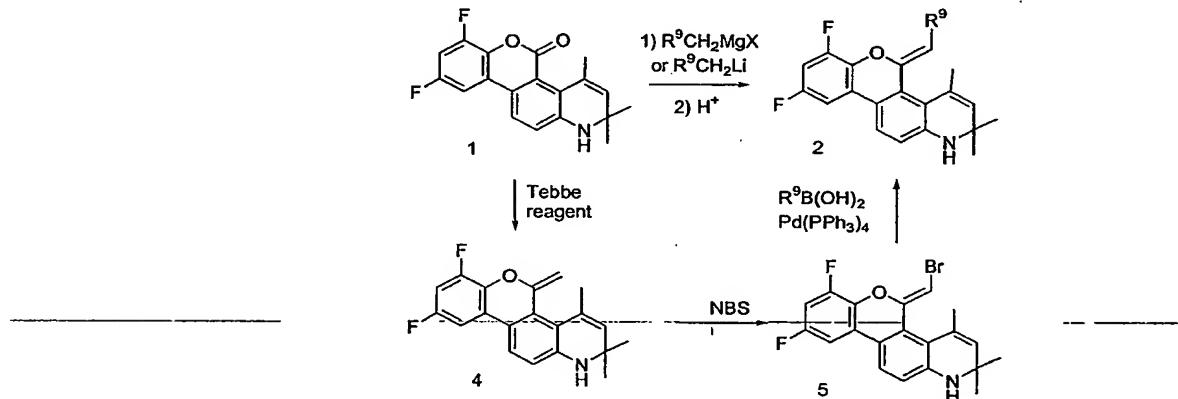
20 (\pm)-7,9-difluoro-5-(3,4-dimethyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 79);

(\pm)-7,9-difluoro-5-(3-(3-bromophenyl)phenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 80); and

7,9-difluoro-5(*Z*)-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 81).

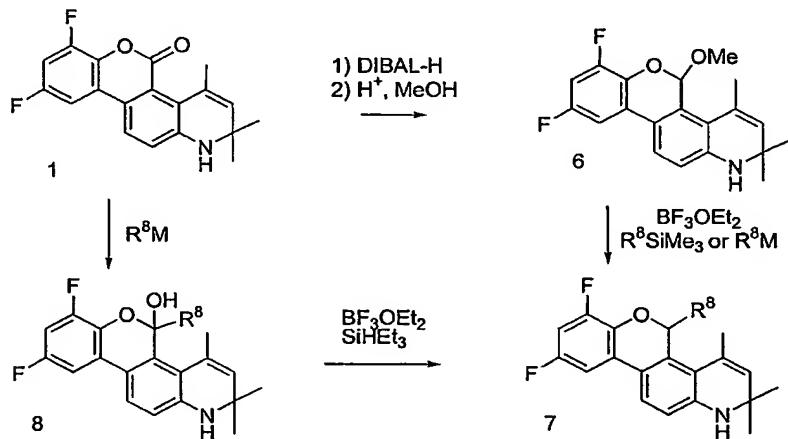
5 The sequence of steps for the general schemes to synthesize the compounds of the present invention is shown below. In each of the Schemes the R groups (e.g., R⁸, R⁹, etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulae I and II also comprise potential 10 substituents for the analogous positions on the structures within the Schemes. In a further aspect, the present invention contains a novel process for the preparation of the compounds of the present invention.

Scheme I



The process of Scheme I begins with addition of organolithium or Grignard reagents to lactones 1 followed by the treatment with a Lewis acid, such as p-toluenesulfonic acid, to produce compounds of structure 2. An alternative route starts with the treatment of lactone 1 with Tebbe reagent to provide compound 4. Bromination with NBS affords the bromomethylidene 5. Palladium catalyzed Suzuki reaction of compound 5 with a boronic acid gives the methylidene derivatives of structure 2.

Scheme II



Scheme II describes the synthesis of the 5-alkyl/aryl analogues 7. Reduction of

lactone 1 with DIBAL-H followed by acid catalyzed methylation provides lactal intermediates 6. Treatment of the lactal 6 with a nucleophile in the presence of a Lewis acid, such as BF₃-OEt₂, affords the final products of structure 7. Alternatively, addition of a nucleophile directly to lactone 1 affords hemiacetals 8, which are treated with silane in the presence of a Lewis acid leading to the same products 7.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

5 As noted above, PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms
10 depending upon the type of administration desired. Suitable administration routes include enteral (e.g., oral), topical, suppository, inhalable and parenteral (e.g., intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, 15 alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical
20 compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio).

5 Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention will 10 generally be administered in the form of a dosage unit (e.g., tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 µg/kg of body weight to about 50 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 2 µg/kg to about 25 mg/kg of body weight. Preferably, the compounds of the present 15 invention are administered in a daily dosage of from about 10 µg/kg to about 5 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

20 Compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. Such compounds are particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

Compounds and pharmaceutical compositions of the present invention may be extremely potent activators of PR. For example, compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 50 nM. Some compounds and compositions of the present invention may display 5 50% maximal activation of PR at a concentration of less than 20 nM, and some may display such activity at a concentration of 10 nM or less. In addition, the compounds of the present invention may be tissue-selective modulators. For example, the compounds of this invention may suppress estrogen-induced endometrial stimulation in uterus equally efficacious as marketed steroidal modulator compounds but display reduced 10 proliferative activity or antagonized endogenous hormone induced proliferative activity in breasts.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

15 Preparation of 7,9-difluoro-5(Z)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 10, Structure 2 of Scheme I, where R⁹ = phenyl).

General procedure I for preparing 5(Z)-substituted methyldene compounds (Structure 2 of Scheme I) from lactones (Structure 1 of Scheme I) and a Grignard or 20 organolithium reagent. To a solution (0.2 – 1.0 M) of lactone 1 in THF was added a freshly prepared Grignard or organolithium solution (3 - 5 equiv.). The reaction mixture was stirred for 1-12 h until the starting material was consumed and then was poured into ice-cold 50% NH₄Cl and extracted with EtOAc (2x). The extracts were washed with

brine (3×), dried (Na_2SO_4) and concentrated. A solution (0.2 – 0.5 M) of the crude lactol intermediate in CH_2Cl_2 was treated with a catalytic amount of p-toluenesulfonic acid at room temperature for 3 h, quenched with saturated NaHCO_3 and extracted with EtOAc (2×). The extracts were washed with brine (3×), dried (5 Na_2SO_4), and concentrated. Flash chromatography (silica gel, EtOAc –hexane 2% to 10% gradient) of the crude mixture afforded the final product in good yield. To prevent photoisomerization of the benzylidene analogues, the dehydration step and the work-up should be carried out in a light-controlled environment.

Compound 10 was prepared from benzyl Grignard and 7,9-difluoro-1,2-dihydro-10 2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 11, structure 1 of Scheme I) according to the general procedure as a yellow solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.84 (d, $J = 7.9$, 2H), 7.40–7.36 (m, 4H), 7.20–7.14 (m, 1H), 6.76–6.71 (m, 1H), 6.66 (d, $J = 8.4$, 1H), 5.67 (s, 1H), 5.54 (s, 1H), 4.24 (bs, 1H), 2.18 (s, 3H), 1.35 (bs, 6H).

EXAMPLE 2

15 Preparation of 7,9-difluoro-5(2)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 12, Structure 2 of Scheme I, where $\text{R}^9 = 2$ -fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1 from 2-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I,) as a 20 yellow solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.44–8.38 (m, 1H), 7.39 (d, $J = 8.4$, 1H), 7.23–7.14 (m, 3H), 7.06–7.00 (m, 1H), 6.76–6.70 (m, 1H), 6.67 (d, $J = 8.4$, 1H), 6.00 (s, 1H), 5.56 (s, 1H), 4.25 (bs, 1H), 2.12 (s, 3H), 1.35 (bs, 6H).

EXAMPLE 3

Preparation of 7,9-difluoro-5(Z)-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 13, Structure 2 of Scheme I, where R⁹ = 2-chlorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2-chlorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) 8.45 (d, *J* = 8.0, 1H), 7.39 (d, *J* = 8.5, 1H), 7.36-7.30 (m, 2H), 7.18-7.13 (m, 2H), 6.73-6.70 (m, 1H), 6.69 (d, *J* = 8.5, 1H), 6.25 (s, 1H), 5.56 (s, 1H), 4.27 (bs, 1H), 2.13 (s, 3H), 1.35 (bs, 6H).

10

EXAMPLE 4

Preparation of 7,9-difluoro-5(Z)-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 14, Structure 2 of Scheme I, where R⁹ = 4-pyridyl).

15 This compound was prepared in a similar fashion as that described in Example 1 from 4-picoly lithium and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) 8.59 (d, *J* = 5.8, 2H), 7.69 (d, *J* = 5.1, 2H), 7.44 (d, *J* = 8.5, 1H), 7.20-7.18 (m, 1H), 6.81-6.79 (m, 1H), 6.73 (d, *J* = 8.5, 1H), 5.63 (s, 1H), 5.58 (s, 1H), 4.31 (bs, 1H), 2.09 (d, *J* = 1.2, 3H), 1.37 (bs, 6H).

EXAMPLE 5

Preparation of 7,9-difluoro-5(Z)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 15, Structure 2 of Scheme I, where R⁹ = 3-fluorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 3-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-d₆) 7.82–7.79 (ddd, *J* = 2.0, 2.0, 9.5, 1H), 7.66 (d, *J* = 8.5, 1H), 7.52–7.38 (m, 3H), 7.05–6.97 (m, 2H), 6.87 (d, *J* = 8.5, 1H), 6.10 (bs, 1H), 5.79 (s, 1H), 5.58 (s, 1H), 2.08 (s, 3H), 1.40 (bs, 6H).

10 EXAMPLE 6

Preparation of 7,9-difluoro-5(Z)-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 16, Structure 2 of Scheme I, where R⁹ = 4-fluorophenyl).

This compound was prepared in a similar fashion as that described in Example 1
15 from 4-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-d₆) 7.92–7.88 (dd, *J* = 5.6, 8.9, 2H), 7.64 (d, *J* = 8.5, 1H), 7.46–7.42 (ddd, *J* = 2.1, 2.1, 9.5, 1H), 7.19–7.14 (dd, *J* = 8.7, 8.7, 2H), 6.98–6.96 (m, 1H), 6.84 (d, *J* = 8.5, 1H), 6.07 (bs, 1H), 5.76 (s, 1H), 5.57 (s, 1H), 2.08 (s, 3H), 1.31 (bs, 6H).

EXAMPLE 7

Preparation of 7,9-difluoro-5(Z)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 17, Structure 2 of Scheme I, where R⁹ = 2,5-difluorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2,5-difluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-*d*₆) 8.26-8.21 (m, 1H), 7.69 (d, *J* = 8.5, 1H), 7.51-7.47 (ddd, *J* = 2.4, 2.4, 9.9, 1H), 7.22-7.16 (ddd, *J* = 4.7, 9.3, 9.3, 1H), 7.09-7.00 (m, 2H), 6.90 (d, *J* = 8.4, 1H), 6.16 (bs, 1H), 6.03 (s, 1H), 5.59 (s, 1H), 2.10 (s, 3H),
10 1.30 (bs, 6H).

EXAMPLE 8

Preparation of 7,9-difluoro-5(Z)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 18, Structure 2 of Scheme I, where R⁹ = 2-methoxyphenyl).

15 This compound was prepared in a similar fashion as that described in Example 1 from 2-methoxybenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-*d*₆) 8.31-8.28 (dd, *J* = 1.6, 7.8, 1H), 7.61 (d, *J* = 8.5, 1H), 7.44-7.41 (ddd, *J* = 2.0, 2.0, 9.9, 1H), 7.26-7.22 (ddd, *J* = 1.7, 7.5, 7.5, 1H), 7.04-6.90 (m, 3H), 6.82 (d, *J* = 8.5, 1H), 6.26 (s, 1H), 6.12 (bs, 1H), 5.55 (s, 1H),
20 3.80 (s, 3H), 2.11 (s, 3H), 1.33 (bs, 6H).

EXAMPLE 9

Preparation of 7,9-difluoro-5(Z)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 19, Structure 2 of Scheme I, where R⁹ = 2-methyl-5-fluorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2-methyl-5-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-*d*₆) 8.14-8.11 (dd, *J* = 2.7, 14.2, 1H), 7.66 (d, *J* = 8.5, 1H), 7.46 (ddd, *J* = 2.2, 2.2, 9.9, 1H), 7.24-7.21 (dd, *J* = 6.3, 8.2, 1H), 7.01-6.96 (ddd, *J* = 3.0, 8.6, 10.4, 1H), 6.94-6.90 (ddd, *J* = 2.8, 8.4, 8.4, 10 1H), 6.88 (d, *J* = 8.5, 1H), 6.12 (s, 1H), 6.03 (s, 1H), 5.59 (s, 1H), 2.27 (s, 3H), 2.12 (s, 3H), 1.34 (bs, 6H).

EXAMPLE 10

Preparation of 7,9-difluoro-5(Z)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 20, Structure 2 of Scheme I, where 15 R⁹ = 3-methyl-4-pyridyl).

This compound was prepared in a similar fashion as that described in Example 1 from 3-methyl-4-picolylium and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (500 MHz, CDCl₃) 8.49 (d, *J* = 4.9, 1H), 8.39 (s, 1H), 8.19 (d, *J* = 5.5, 1H), 7.43 (d, *J* = 8.5, 1H), 7.17 (ddd, *J* = 9.5, 2.4, 2.1, 1H), 6.77 (ddd, *J* = 10.1, 8.5, 3.1, 20 1H), 6.73 (d, *J* = 8.5, 1H), 5.92 (s, 1H), 5.56 (s, 1H), 4.31 (bs, 1H), 2.24 (s, 3H), 2.12 (d, *J* = 1.2, 3H), 1.38 (bs, 6H).

EXAMPLE 11

Preparation of 7,9-difluoro-5(Z)-(2-methyl-3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 21, Structure 2 of Scheme I, where R⁹ = 2-methyl-3-fluorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2-methyl-3-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-*d*₆) 8.06 (d, *J* = 7.8, 1H), 7.66 (d, *J* = 8.5, 1H), 7.47-7.43 (ddd, *J* = 2.2, 2.2, 9.9, 1H), 7.31-7.26 (dd, *J* = 7.9, 14.0, 1H), 7.01-6.93 (m, 2H), 6.87 (d, *J* = 8.5, 1H), 6.11 (bs, 1H), 6.02 (s, 1H), 5.59 (s, 1H), 2.20 (s, 10 3H), 2.13 (s, 3H), 1.33 (bs, 6H).

EXAMPLE 12

Preparation of 7,9-difluoro-5(Z)-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 22, Structure 2 of Scheme I, where R⁹ = 3-methyl-2-pyridyl).

15 This compound was prepared in a similar fashion as that described in Example 1 from 3-methyl-2-picoly lithium and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (500 MHz, CDCl₃) 8.50 (dd, *J* = 4.6, 1.5, 1H), 7.50 (dd, *J* = 7.6, 1.5, 1H), 7.40 (d, *J* = 8.5, 1H), 7.15-7.12 (m, 1H), 7.07 (dd, *J* = 7.6, 4.6, 1H), 6.69 (d, *J* = 8.5, 1H), 6.66 (ddd, *J* = 10.2, 8.2, 2.7, 1H), 6.01 (s, 1H), 5.53 (d, *J* = 1.2, 1H), 4.26 (bs, 1H), 2.38 (s, 3H), 2.26 (d, *J* = 1.2, 3H), 1.33 (bs, 6H).

EXAMPLE 13

Preparation of 7,9-difluoro-5(Z)-(2,3-dimethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 23, Structure 2 of Scheme I, where R⁹ = 2,3-dimethylphenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2,3-dimethylbenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-*d*₆) 7.97 (d, *J* = 7.7, 1H), 7.63 (d, *J* = 8.5, 1H), 7.44-7.41 (ddd, *J* = 2.2, 2.2, 10.1, 1H), 7.16-7.13 (dd, *J* = 7.6, 7.6, 1H), 7.07 (d, *J* = 7.3, 1H), 6.94-6.89 (ddd, *J* = 2.9, 8.9, 11.0, 1H), 6.84 (d, *J* = 8.5, 1H), 6.07 (bs, 1H),
10 6.05 (s, 1H), 5.70 (s, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 1.30 (bs, 6H).

EXAMPLE 14

Preparation of 7,9-difluoro-5(Z)-cyanomethylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 24, Structure 2 of Scheme I, where R⁹ = cyano).

15 This compound was prepared in a similar fashion as that described in Example 1 from acetonitrile lithium and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H NMR (500 MHz, CDCl₃) 7.50 (d, *J* = 8.6, 1H), 7.24-7.19 (m, 1H), 6.87-6.81 (m, 1H), 6.83 (d, *J* = 8.6, 1H), 5.58 (s, 1H), 4.76 (s, 1H), 4.40 (s, 1H), 2.11 (d, *J* = 1.2, 3H), 1.57 (bs, 6H).

EXAMPLE 15

Preparation of 7,9-difluoro-5(Z)-hexylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 25, Structure 2 of Scheme I, where R⁹ = pentyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from n-hexyl lithium and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (500 MHz, CDCl₃) 7.32 (d, *J* = 8.2, 1H), 7.10 (ddd, *J* = 9.8, 2.7, 1.8, 1H), 6.69 (ddd, *J* = 10.4, 8.5, 2.7, 1H), 6.59 (d, *J* = 8.5, 1H), 5.49 (s, 1H), 4.86 (t, *J* = 7.9, 1H), 4.15 (bs, 1H), 2.35-2.27 (m, 2H), 2.08 (d, *J* = 1.2, 3H), 1.74-1.64 (m, 4H), 1.63-1.58 (m, 1H), 10 1.36-1.25 (m, 8H), 1.20-1.13 (m, 4H), 1.00-1.93 (m, 2H).

EXAMPLE 16

Preparation of 7,9-difluoro-5(Z)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 26, Structure 2 of Scheme I, where R⁹ = 2-methoxy-5-fluorophenyl).

15 This compound was prepared in a similar fashion as that described in Example 1 from 2-methoxy-5-fluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, Acetone-d₆) 8.15-8.12 (ddd, *J* = 1.6, 1.6, 10.6, 1H), 7.63 (d, *J* = 8.5, 1H), 7.46-7.43 (ddd, *J* = 2.2, 2.2, 10.2, 1H), 7.00-6.95 (m, 3H), 6.86-6.84 (d, *J* = 8.4, 1H), 6.27 (s, 1H), 6.06 (bs, 1H), 5.56 (s, 1H), 3.81 (s, 3H), 20 2.09 (s, 3H), 1.19 (bs, 6H).

EXAMPLE 17

Preparation of 7,9-difluoro-5(Z)-(2,4,5-trifluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 27, Structure 2 of Scheme I, where R⁹ = 2,4,5-trifluorophenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2,4,5-trifluorobenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (500 MHz, CDCl₃) 8.38-8.32 (m, 1H), 7.41 (d, J = 8.2, 1H), 7.18-7.16 (m, 1H), 6.93-6.87 (m, 1H), 6.79-6.75 (m, 1H), 6.69 (d, J = 8.2, 1H), 5.88 (s, 1H), 5.56 (s, 1H), 4.28 (bs, 1H), 2.08 (s, 3H), 1.34 (bs, 6H).

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EXAMPLE 18

Preparation of 7,9-difluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 28, Structure 4 of Scheme I).

Treatment of Compound 11 (Structure 1 of Scheme I, where R⁶ = methyl) with Tebbe reagent (0.5 M in toluene) afforded compound 28 as a yellow solid: ¹H-NMR (500 MHz, CDCl₃) 7.35 (d, J = 8.2, 1H), 7.13 (ddd, J = 9.8, 2.4, 2.1, 1H), 6.71 (ddd, J = 10.1, 8.5, 2.8, 1H), 6.65 (d, J = 8.2, 1H), 5.51 (d, J = 0.9, 1H), 5.19 (d, J = 1.5, 1H), 4.52 (d, J = 1.5, 1H), 4.20 (bs, 1H), 2.14 (d, J = 1.2, 3H), 1.30 (bs, 6H).

EXAMPLE 19

20 Preparation of 7,9-difluoro-5(Z)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 29, Structure 5 of Scheme I).

Treatment of Compound 28 (Structure 4 of Scheme I) with NBS in DMF at rt for 10 min and standard work-up followed by chromatography provided compound 29 as a yellow foam: ¹H-NMR (500 MHz, CDCl₃) 7.38 (d, J = 8.2, 1H), 7.15-7.11 (m, 1H), 6.75

(ddd, $J = 10.1, 8.2, 2.7, 1\text{H}$), 6.67 (d, $J = 8.2, 1\text{H}$), 5.54 (s, 1H), 5.53 (s, 1H), 4.24 (bs, 1H), 2.08 (d, $J = 1.5, 3\text{H}$), 1.30 (bs, 6H).

EXAMPLE 20

Preparation of 7,9-difluoro-5(Z)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-

5 trimethyl-5H-chromeno[3,4-f]quinoline (Compound 30, Structure 2 of Scheme I, $\text{R}^9 = 3\text{-thiophene}$).

To a solution of compound 29 (Structure 5 of Scheme I) in DME was added Pd(PPh_3)₄ (3 mol%) and the mixture was stirred at rt for 15 min. A solution of 3-thiopheneboronic acid in DME and CsF were added to the reaction mixture. The 10 reaction was heated at 80°C for 2 h, quenched with NaHCO_3 (sat'd aqueous) and extracted with EtOAc. Removal of solvent and chromatography of the crude mixture afforded 30 as yellow foam: ¹H-NMR (500 MHz, CDCl_3) 7.77 (d, $J = 2.4, 1\text{H}$), 7.54 (d, $J = 4.0, 1\text{H}$), 7.37 (d, $J = 8.2, 1\text{H}$), 7.32 (dd, $J = 4.9, 3.1, 1\text{H}$), 7.17-7.13 (m, 1H), 6.76-6.72 (m, 1H), 6.65 (d, $J = 8.2, 1\text{H}$), 5.76 (s, 1H), 5.54 (s, 1H), 4.23 (bs, 1H), 2.09 (d, $J = 0.9, 3\text{H}$), 1.34 (bs, 6H).

EXAMPLE 21

Preparation of 7,9-difluoro-5(Z)-(2-thienylmethylidene)-1,2-dihydro-2,2,4- trimethyl-5H-chromeno[3,4-f]quinoline (Compound 31, Structure 2 of Scheme I, $\text{R}^9 = 2\text{-thiophene}$).

20 This compound was prepared in a similar fashion as that described in Example 20 from compound 29 (Structure 5 of Scheme I) and 2-thiopheneboronic acid as yellow foam: ¹H-NMR (500 MHz, CDCl_3) 7.39 (d, $J = 8.5, 1\text{H}$), 7.33 (d, $J = 4.9, 1\text{H}$), 7.23 (d, J

= 3.7, 1H), 7.16-7.13 (m, 1H), 7.05 (dd, J = 5.2, 3.7, 1H), 6.78-6.74 (m, 1H), 6.65 (d, J = 8.2, 1H), 5.99 (s, 1H), 5.56 (s, 1H), 4.25 (bs, 1H), 2.09 (d, J = 0.9, 3H), 1.36 (bs, 6H).

EXAMPLE 22

Preparation of (\pm)-7,9-difluoro-5-methoxy-1,2-dihydro-2,2,4-trimethyl-5H-

5 chromeno[3,4-f]quinoline (Compound 32, Structure 6 of Scheme II).

Reduction of Compound 11 (Structure 1 of Scheme II) with DIBAL-H in toluene at -78°C for 1 h provided a lactal intermediate, which, upon treatment with TsOH in methanol, afforded Compound 32 as a white solid: ^1H NMR (500 MHz, CDCl_3) 7.39 (d, J = 8.6, 1H), 7.21 (dt, J = 8.8, 2.4, 1H), 6.75 (td, J = 9.3, 2.7, 1H), 6.60 (d, J = 8.2, 1H), 10 6.40 (s, 1H), 5.53 (d, J = 1.5, 1H), 4.04 (s, 1H), 3.49 (s, 3H), 2.27 (d, J = 1.2, 3H), 1.34 (s, 3H), 1.20 (s, 3H).

EXAMPLE 23

Preparation of (\pm)-7,9-difluoro-5-phenyl-1,2-dihydro-2,2,4-trimethyl-5H-

chromeno[3,4-f]quinoline (Compound 33, Structure 7 of Scheme II, where

15 R^8 = phenyl).

This compound was prepared by the following general procedure:

To a stirred solution of bromobenzene in THF at -78 °C under nitrogen atmosphere was added n-BuLi in hexanes (1.6 M). After one hour a solution of compound 11 (structure 1 of Scheme II) in THF was added dropwise and after 2 hours at 20 -78 °C the temperature was allowed to rise to -55 °C. The reaction mixture was stirred for an additional hour at this temperature, poured into an aqueous ammonium chloride solution and extracted twice with ethyl acetate. The organic extracts were washed with brine, combined, dried (Na_2SO_4), concentrated and purified using column

chromatography on silica gel (heptanes/ ethyl acetate: gradient 20/1 to 10/1) to give structure 8 of Scheme II (R^8 = Phenyl) as an oil. This oil was dissolved in dichloromethane, and 0.2 mL of triethylsilane and 0.17 mL of boron trifluoride diethyl etherate were added. After stirring for 6 hours a saturated solution of sodium

5 hydrogencarbonate was added and extracted three times with dichloromethane. The organic extracts were combined, dried (Na_2SO_4) and concentrated. Purification using HPLC (LUNA C18(2), CH_3CN /water, gradient 6/4 to 10/0) yielded compound 33 as a solid: 1H NMR (400 MHz, $DMF-d_7$) 7.70 (d, J = 8.8, 1H), 7.40 (dq, J = 10, 1.8, 1H), 7.30 (M, 5H), 7.10 (s, 1H), 6.93 (d, J = 8.8, 1H), 6.92 (M, 1H), 6.54 (d, J = 1.6, 1H),
10 5.52 (t, J = 1.6, 1H), 2.30 (d, J = 1.2, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

EXAMPLE 24

Preparation of (\pm)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 34, Structure 7 of Scheme II, where R^8 = 3-methylbenzene).

15 Compound 34 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 3-bromotoluene as a solid: 1H NMR (400 MHz, $DMF-d_7$) 7.85 (d, J = 8.6, 1H), 7.56 (dq, J = 10, 1.8, 1H), 7.37 (t, J = 7.6, 1H), 7.30 (s, 1H), 7.25 (d, J = 7.8, 1H), 7.23 (s, 1H), 7.21 (d, J = 8, 1H), 7.09 (d, J = 8.8, 1H), 7.09 (M, 1H), 6.70 (s, 1H), 5.69 (t, J = 1.6, 1H), 2.41 (s, 3H), 2.21 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H).

EXAMPLE 25

Preparation of (\pm)-7,9-difluoro-5-(1,3-benzodioxol-5-yl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 35, Structure 7 of Scheme II, where $R^8 = 5$ -(1,3-benzodioxole)).

5 Compound 35 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 5-bromo[1,3]benzodioxole as a solid: 1H NMR (400 MHz, DMF- d_7) 7.85 (d, $J = 8.6$, 1H), 7.75 (dq, $J = 10, 1.8$, 1H), 7.16 (s, 1H), 7.10 (m, 1H), 7.08 (d, $J = 8.8$, 1H), 7.04 (d, $J = 1.6$, 1H), 6.96 (d, $J = 8.8$, 1H), 6.8 (dd, $J = 8.2, 1.8$, 1H), 6.69 (d, $J = 1.8$, 1H), 6.21 (s, 2H), 5.68 (t, $J = 1.6$, 1H), 2.22 (s, 10 3H), 1.45 (s, 3H), 1.42 (s, 3H).

EXAMPLE 26

Preparation of (\pm)-7,9-difluoro-5-(4-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 36, Structure 7 of Scheme II, where $R^8 = 4$ -bromobenzene).

15 Compound 36 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 1,4-dibromobenzene as a solid: 1H NMR (500 MHz, $CDCl_3$) 7.38 (d, $J = 8.4$, 1H), 7.33 (m, 2H), 7.1 (m, 2H), 6.99 (dq, $J = 9.6, 2$, 1H), 6.91 (s, 1H), 6.69 (d, $J = 8.8$, 1H), 6.56 (m, 1H), 5.48 (s, 1H), 4.06 (s, 1H), 1.97 (s, 1H), 1.30 (s, 3H), 1.26 (s, 3H).

EXAMPLE 27

Preparation of (\pm)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 37, Structure 7 of Scheme II, where, R^8 = 4-chloro-3-methylbenzene).

5 Compound 37 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 5-bromo-2-chlorotoluene as a solid: 1H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H), 2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

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EXAMPLE 28

Preparation of (-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline and (+)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compounds 38 and 39, Structure 7 of Scheme II, where R^8 = 4-chloro-3-methylbenzene).

15

These compounds were isolated as enantiomers of Compound 37 by a chiral HPLC separation. Retention times: OJ column 0.46 cm x 25 cm, flow 1ml/min, heptanes/ethanol 85/15; R_t = 12 min and 15 min. Compound 38 is the (-)-isomer: 1H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H),

20

2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); Compound 39 is the (+)-isomer: 1H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.4, 1H), 7.15 (d, 8.8, 1H), 7.09 (d, J = 2, 1H), 6.98 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 8.8, 1H), 6.57 (m, 1H), 5.49 (s, 1H), 4.06 (s, 1H), 2.24 (s, 1H), 1.98 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

EXAMPLE 29

Preparation of (\pm)-7,9-difluoro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 40, Structure 7 of Scheme II, where R⁸ = 3-fluorobenzene).

5 Compound 40 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 3-bromofluorobenzene as a solid: ¹H NMR (500 MHz, CDCl₃) 7.38 (d, *J* = 8.4, 1H), 7.18 (m, 1H), 7.05 (d, *J* = 8.2, 1H), 7.0 (dq, *J* = 10, 2, 1H), 6.95 (s, 1H), 6.89 (m, 2H), 6.70 (d, *J* = 8.6, 1H), 6.57 (m, 1H), 5.49 (d, *J* = 1.4, 1H), 4.06 (s, 1H), 1.99 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H).

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EXAMPLE 30

Preparation of (\pm)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 41, Structure 7 of Scheme II, where R⁸ = 3-chlorobenzene).

15 Compound 41 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 3-bromochlorobenzene as a solid: ¹H NMR (500 MHz, DMSO-*d*₆) 7.59 (d, *J* = 8.8, 1H), 7.36 (dq, *J* = 10.4, 1.8, 1H), 7.31 (m, 2H), 7.14 (s, 1H), 7.10 (m, 1H), 7.0 (s, 1H), 6.96 (m, 1H), 6.79 (d, *J* = 8.8, 1H), 6.57 (d, *J* = 2, 1H), 5.44 (t, *J* = 1.6, 1H), 1.90 (d, *J* = 1.4, 3H), 1.22 (s, 3H), 1.19 (s, 3H).

EXAMPLE 31

Preparation of (\pm)-7,9-difluoro-5-(3-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 42, Structure 7 of Scheme II, where R^8 = 3-bromobenzene).

5 Compound 42 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 1,3-dibromobenzene as a solid: 1H NMR (600 MHz, DMF- d_6) 7.88 (d, J = 8.7, 1H), 7.67 (d, J = 8.4, 1H), 7.61 (s, 1H), 7.59 (dq, J = 10.2, 2.1, 1H), 7.50 (t, J = 7.8, 1H), 7.46 (d, J = 7.8, 1H), 7.30 (s, 1H), 7.13 (m, 1H), 7.11 (d, J = 8.7, 1H), 6.77 (s, 1H), 5.72 (s, 1H), 2.22 (s, 3H), 1.47 (s, 3H), 1.44 (s, 10 3H).

EXAMPLE 32

Preparation of (\pm)-7,9-difluoro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 43, Structure 7 of Scheme II, where R^8 = 4-chlorobenzene).

15 Compound 43 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 4-bromochlorobenzene as a solid: 1H NMR (500 MHz, CDCl₃) 7.38 (d, J = 8.4, 1H), 7.17 (M, 4H), 6.99 (dq, J = 9.6, 2, 1H), 6.92 (s, 1H), 6.69 (d, J = 8.6, 1H), 6.56 (m, 1H), 5.48 (s, 1H), 4.45 (s, 1H), 1.97 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H).

EXAMPLE 33

Preparation of (\pm)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5H-chromeno[3,4-f]quinoline (Compound 44, Structure 7 of Scheme II, where R^8 = methyl).

5 Compound 44 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and methylolithium as a solid: 1H NMR (500 MHz, DMF- d_7) 7.54 (d, J = 8.8, 1H), 7.41 (dq, J = 10, 2, 1H), 7.02 (m, 1H), 6.74 (d, J = 8.8, 1H), 6.36 (s, 1H), 6.16 (q, J = 6.4, 1H), 5.50 (m, 1H), 2.23 (s, 3H), 1.32 (d, J = 6.6, 3H), 1.21 (s, 3H), 1.16 (s, 3H).

10 EXAMPLE 34

Preparation of (\pm)-7,9-difluoro-5-(2-oxo-2-phenylethyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 45, Structure 7 of Scheme II, where R^8 = 2-oxo-2-phenylethyl).

To a stirred solution of 0.31 mmol of compound 32 (Structure 6 of Scheme II) in
15 10 mL of dichloromethane and 0.3 mL of 1-phenyl-1-trimethylsilyloxyethene at -78 °C under a nitrogen atmosphere was added 0.22 mL of boron trifluoride diethyl etherate. After stirring for 30 minutes a saturated aqueous solution of sodium hydrogencarbonate was added and the resulting mixture was extracted three times with dichloromethane. The organic extracts were combined, dried (Na_2SO_4) and concentrated. Purification using
20 column chromatography on silica gel (toluene) and then HPLC (LUNA C18(2), CH₃CN/water, gradient 95/5 to 100/0) yielded 50 mg of compound 45 as a solid: 1H NMR (500 MHz, DMF- d_7) 7.91 (dd, J = 8.8, 1.2, 2H), 7.64 (d, J = 8.6, 1H), 7.64 (tt, J = 7.4, 1H), 7.50 (d, J = 8.4, 1H), 7.49 (m, 2H), 6.95 (m, 1H), 6.80 (dd, 1H), 6.82 (d, J =

8.4, 1H), 6.46 (d, J = 2, 1H), 5.55 (t, J = 1.8, 1H), 3.92 (dd, J = 17.4, 10, 1H), 3.02, (dd, J = 17.4, 2.4, 1H), 2.31, (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H).

EXAMPLE 35

Preparation of (\pm)-7,9-difluoro-5-ethyl-1,2-dihydro-2,2,4-trimethyl-5H-

5 chromeno[3,4-f]quinoline (Compound 46, Structure 7 of Scheme II, where R^8 = ethyl).

Hydrogenation at atmospheric pressure of compound 47 in ethyl acetate using PtO₂ as catalyst and purification using HPLC (LUNA C18(2), CH₃CN/water) yielded compound 46 as a solid: ¹H NMR (500 MHz, DMF-*d*₇) 7.57 (d, J = 8.4, 1H), 7.43 (dq, J = 10.2, 1.8, 1H), 7.05 (m, 1H), 6.77 (d, J = 8.6, 1H), 6.39 (d, J = 1.6, 1H), 5.87 (dd, J = 10.2, 3.6, 1H), 5.54 (t, J = 1.8, 1H), 2.25 (d, J = 1.4, 3H), 1.74 (m, 1H), 1.52 (m, 1H), 1.27 (s, 3H), 1.18 (s, 3H), 1.00 (t, J = 7.4, 3H).

EXAMPLE 36

Preparation of (\pm)-7,9-difluoro-5-ethenyl-1,2-dihydro-2,2,4-trimethyl-5H-

15 chromeno[3,4-f]quinoline (Compound 47, Structure 7 of Scheme II, where R^8 = vinyl).

Compound 47 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and tributyl(ethenyl)tin as a solid: ¹H NMR-(600 MHz, DMF-*d*₇) 7.78 (d, J = 8.7, 1H), 7.59 (dt, J = 10.2, 1H), 7.21 (m, 1H), 7.11 (d, J = 8.4, 1H), 6.67 (m, 1H), 6.61 (s, 1H), 6.23 (m, 1H), 5.72 (s, 1H), 5.45 (dt, J = 10.8, 1H), 5.15 (dt, J = 17.7, 1H), 2.41 (s, 3H), 1.43 (s, 6H).

EXAMPLE 37

Preparation of (\pm)-7,9-difluoro-5-(2-oxo-3-butenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-*f*]quinoline (Compound 48, Structure 7 of Scheme II, where R⁸ = 2-oxo-3-butenyl).

5 Compound 48 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-trimethylsilyloxy-1,3-butadiene as a solid: ¹H NMR (600 MHz, DMF-*d*₇) 7.61 (d, *J* = 8.7, 1H), 7.47 (dt, *J* = 10.5, 2.4, 1H), 7.02 (m, 1H), 6.80 (d, *J* = 8.7, 1H), 6.64 (dd, *J* = 10.5, 2.7, 1H), 6.45 (s, 1H), 6.40 (dd, *J* = 17.7, 11.1, 1H), 6.16 (d, *J* = 18, 1H), 5.91 (d, *J* = 11.4, 1H), 5.55 (s, 1H), 3.48 (dd, 1H), 2.62 (dd, *J* = 17.1, 2.7, 1H), 2.29 (s, 3H), 1.26 (s, 3H), 1.18 (s, 3H).

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EXAMPLE 38

Preparation of Methyl (\pm)-7,9-difluoro-1,2-dihydro- $\alpha,\alpha,2,2,4$ -pentamethyl-5H-chromeno[3,4-*f*]quinoline-5-ethanoate (Compound 49, Structure 7 of Scheme II, where R⁸ = 1-methoxycarbonyl-1-methylethyl).

15 Compound 49 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 1-methoxy-2-methyl-1-trimethylsilyloxypropene as a solid: ¹H NMR (600 MHz, DMF-*d*₇) 7.86 (d, *J* = 8.7, 1H), 7.64 (dt, *J* = 5.3, 1.8, 1H), 7.21 (m, 1H), 7.04 (d, *J* = 8.4, 1H), 6.80 (s, 1H), 6.48 (s, 1H), 5.73 (s, 1H), 3.81 (s, 3H), 2.49 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.10 (s, 3H).

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EXAMPLE 39

Preparation of (\pm)-7,9-difluoro-5-ethynyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 50, Structure 7 of Scheme II, where R⁸ = acetylene).

5 Compound 50 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and ethynyltributyltin as a solid: ¹H NMR (400 MHz, DMF-*d*₇) 7.77 (d, *J* = 8.6, 1H), 7.66 (dt, *J* = 10, 1.6, 1H), 7.29 (m, 1H), 7.00 (d, *J* = 8.4, 1H), 6.86 (d, *J* = 2.2, 1H), 6.70 (s, 1H), 5.74 (s, 1H), 3.81 (dd, *J* = 2.4, 0.8, 1H), 2.59 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H).

10 **EXAMPLE 40**

Preparation of (\pm)-7,9-difluoro-5-cyano-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 51, Structure 7 of Scheme II, where R⁸ = cyano).

15 Compound 51 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and trimethylsilyl cyanide as a solid: ¹H NMR (400 MHz, DMF-*d*₇) 7.56 (d, *J* = 8.8, 1H), 7.46 (dq, *J* = 10, 1.8, 1H), 7.1 (m, 1H), 7.04 (s, 1H), 6.79 (d, *J* = 8.8, 1H), 6.64 (s, 1H), 5.50 (q, 1H), 2.26 (s, 3H), 1.20 (s, 3H), 1.06 (s, 3H).

EXAMPLE 41

Preparation of (\pm)-7,9-difluoro-5-butyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 52, Structure 7 of Scheme II, where R⁸ = butyl).

5 Compound 52 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and n-butyllithium as a solid: ¹H NMR (600 MHz, DMF-*d*₇) 7.60 (d, *J* = 7.1, 1H), 7.46 (d, *J* = 7.1, 1H), 7.08 (m, 1H), 6.80 (d, *J* = 5.7, 1H), 6.42 (s, 1H), 5.98 (d, *J* = 7.1, 1H), 5.57 (s, 1H), 2.28 (s, 3H), 1.78 (m, 1H), 1.48 (m, 3H), 1.3 (m, 2H), 1.3 (s, 3H), 1.20 (s, 3H), 0.86 (t, *J* = 4.2, 3H).

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EXAMPLE 42

Preparation of (\pm)-7,9-difluoro-5-(2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 53, Structure 7 of Scheme II, where R⁸ = 2-thiophene).

15 Compound 53 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-(tributylstanny)thiophene as a solid: ¹H NMR (600 MHz, DMF-*d*₇) 7.80 (d, *J* = 8.7, 1H), 7.53 (dd, *J* = 5.4, 1.2, 1H), 7.43 (d, *J* = 10.2, 1H), 7.26 (s, 1H), 6.96 (m, 1H), 6.93 (m, 1H), 6.91 (d, *J* = 8.7, 1H), 6.78 (d, *J* = 3.6, 1H), 6.52 (s, 1H), 5.57 (s, 1H), 2.14 (s, 3H), 1.27 (s, 6H).

EXAMPLE 43

Preparation of (\pm)-7,9-difluoro-5-(2-furyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 54, Structure 7 of Scheme II, where $R^8 = 2\text{-furyl}$).

5 Compound 54 was prepared in a similar fashion as that described in Example 23 from Compound 32 (Structure 6 of Scheme II) and 2-(tributylstannyl)furan as a solid: ^1H NMR (600 MHz, DMF- d_7) 7.69 (s, 1H), 7.65 (d, $J = 8.7$, 1H), 7.44 (dt, $J = 11.4$, 1H), 6.99 (s, 1H), 6.94 (m, 1H), 6.88 (d, 8.4, 1H), 6.48 (s, 1H), 6.30 (q, $J = 1.5$, 1H), 5.92 (d, $J = 3.3$, 1H), 5.49 (s, 1H), 2.10 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H).

10 EXAMPLE 44

Preparation of (\pm)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 55, Structure 7 of Scheme II, where $R^8 = \text{allyl}$).

15 Compound 55 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and allyltrimethylsilane as a solid: ^1H NMR (400 MHz, DMF- d_7) 7.78 (d, $J = 8.6$, 1H), 7.64, (dq, $J = 10.2$, 1.8, 1H), 7.24 (m, 1H), 6.97 (d, $J = 8.6$, 1H), 6.61 (d, $J = 1.6$, 1H), 6.24 (dd, $J = 10$, 4, 1H), 6.09 (m, 1H), 6.73 (t, $J = 1.6$, 1H), 5.27 (m, 1H), 5.23 (m, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.44 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H).

EXAMPLE 45

Preparation of (\pm)-7,9-difluoro-5-[3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 56, Structure 7 of Scheme II, where R^8 = 3-trifluoromethylphenyl).

5 Compound 56 was prepared in a similar fashion as that described in Example 23 from Compound 11 (Structure 1 of Scheme II) and 3-bromobenzotrifluoride as a solid: 1H NMR (400 MHz, DMF- d_7) 7.87 (d, J = 8.6, 1H), 7.84 (m, 1H), 7.78 (t, J = 7.6, 2H), 7.72 (m, 1H), 7.57 (dq, J = 10, 1.8, 1H), 7.38 (s, 1H), 7.12 (m, 1H), 7.11 (d, J = 8.6, 1H), 6.78 (d, J = 2, 1H), 6.71 (t, J = 1.6, 1H), 2.21 (d, J = 1.4, 3H), 1.45 (s, 3H), 1.44 (s, 3H).

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EXAMPLE 46

Preparation of Ethyl (\pm)-7,9-difluoro-1,2-dihydro- α -methylene-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline-5-propanoate (Compound 57, Structure 7 of Scheme II, where R^8 = 2-ethoxycarbonyl-2-propenyl).

15 Compound 57 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and ethyl 2-(trimethylsilylmethyl)acrylate as a solid: 1H NMR (600 MHz, DMF- d_7) 7.52 (d, J = 8.7, 1H), 7.38 (dq, J = 10.2, 1.8, 1H), 6.94 (m, 1H), 6.69 (d, J = 8.4, 1H), 6.35 (d, J = 1.5, 1H), 6.17 (dd, J = 10.5, 4.2, 1H), 6.12 (d, J = 1.2, 1H), 5.45 (s, 1H), 5.40 (s, 1H), 4.12 (m, 2H), 2.57 (dd, J = 15, 10.5, 1H), 2.44 (dd, J = 15, 3.9, 1H), 2.23 (s, 3H), 1.21 (s, 3H), 1.18, (t, J = 7.2, 3H), 1.06 (s, 3H).

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EXAMPLE 47

Preparation of (\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5H-chromeno[3,4- β]quinoline-5-propanol (Compound 58, Structure 7 of Scheme II, where R^8 = 2-hydroxymethyl-2-propenyl).

5 To a solution of 64 mg of compound 59 (Structure 7 of Scheme II, where R^8 = 2-acetyloxymethyl-2-propenyl) in 2 mL of methanol, 0.5 mL of THF and 0.5 mL of aqueous 20% KOH stirred at room temperature for 3 hours 2 M hydrochloric acid was added to adjust the pH to 7. A saturated solution of sodium hydrogencarbonate was added and the resulting mixture was extracted with ethyl acetate. The organic extract was 10 dried (Na_2SO_4) and concentrated to yield 60 mg of compound 58 as a solid: 1H NMR (400 MHz, $DMF-d_7$) 7.46 (dd, J = 8.6, 1.8, 1H), 7.32 (dq, J = 10, 1.8, 1H), 6.90 (m, 1H), 6.65 (dd, J = 8.4, 1.8, 1H), 6.11 (d, J = 10.6, 1H), 5.40 (s, 1H), 4.98 (s, 1H), 4.66 (s, 1H), 4.20 (d, J = 14.2, 1H), 3.90 (d, J = 14.2, 1H), 2.36 (dd, J = 15.6, 10.8, 1H), 2.17 (s, 3.5H), 2.13 (s, 0.5H), 1.14 (s, 3H), 1.05 (s, 3H).

15 EXAMPLE 48

Preparation of (\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5H-chromeno[3,4- β]quinoline-5-propanol acetate (Compound 59, Structure 7 of Scheme II, where R^8 = 2-acetyloxymethyl-2-propenyl).

Compound 59 was prepared by a similar procedure as described in Example 34
20 from Compound 32 (Structure 6 of Scheme II) and ethyl 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate as a solid: 1H NMR (600 MHz, $DMF-d_7$) 7.63 (d, J = 8.7, 1H), 7.49 (d, J = 9.9, 1H), 7.07 (m, 1H), 6.82 (d, J = 8.7, 1H), 6.45 (s, 1H), 6.26 (dd, J = 10.8, 2.7, 1H), 5.58 (s, 1H), 5.23 (s, 1H), 5.05 (s, 1H), 4.71 (d, J = 13.5, 1H), 4.60 (d, J = 13.5,

1H), 2.63 (dd, $J = 16.2, 11.1$, 1H), 2.35 (s, 1H), 2.32 (s, 3H), 2.08 (s, 3H), 1.29 (s, 3H), 1.22 (s, 3H).

EXAMPLE 49

Preparation of (\pm)-7,9-difluoro-5-(1-methylethenyl)-1,2-dihydro-2,2,4-trimethyl-

5 5H-chromeno[3,4-f]quinoline (Compound 60, Structure 7 of Scheme II, where $R^8 = 1$ -methylvinyl).

Compound 60 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and (propen-2-yl)tributyltin as a solid: 1H NMR (600 MHz, DMF- d_7) 7.76 (d, $J = 8.3$, 1H), 7.57 (dq, $J = 10.2, 1.8$, 1H), 7.21 (m, 1H), 7.02 (d, $J = 8.7$, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 5.60 (m, 1H), 5.23 (s, 1H), 4.63 (s, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H).

EXAMPLE 50

Preparation of (\pm)-7,9-difluoro-5-(N-methyl-2-pyrrolyl)-1,2-dihydro-2,2,4-

trimethyl-5H-chromeno[3,4-f]quinoline (Compound 61, Structure 7 of Scheme II,

15 where $R^8 = N$ -methyl-2-pyrrolyl).

Compound 61 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and N-methyl-2-(tributylstannyl)pyrrole as a solid: 1H NMR (400 MHz, DMF- d_7) 7.65 (dd, $J = 8.6, 2$, 1H), 7.43 (m, 1H), 7.05 (s, 1H), 6.92 (m, 1H), 6.89 (m, 1H), 6.81 (m, 1H), 6.43 (s, 1H), 5.74 (m, 1H), 5.48 (m, 1H), 5.42 (m, 1H), 3.95 (m, 3H), 1.98 (d, $J = 2$, 3H), 1.29 (d, $J = 2.2$, 3H), 1.21 (d, 3H).

EXAMPLE 51

Preparation of (\pm)-7,9-difluoro-5-phenylethynyl-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 62, Structure 7 of Scheme II, where R^8 = phenylacetylene).

5 Compound 62 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and (phenylethynyl)tributyltin as a solid: 1H NMR (400 MHz, DMF- d_7) 7.64 (dd, J = 8.6, 1H), 7.52 (m, 1H), 7.37 (m, 3H), 7.28 (m, 2H), 7.14 (m, 1H), 6.92 (d, J = 3, 1H), 6.86 (m, 1H), 6.76 (s, 1H), 5.60 (s, 1H), 2.49 (d, J = 1.8, 3H), 1.35 (d, J = 2, 3H), 1.22 (d, J = 2.2, 3H).

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EXAMPLE 52

Preparation of (\pm)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 63, Structure 7 of Scheme II, where R^8 = 2-benzo[b]thiophene).

15 Compound 63 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-(tributylstannyl)benzo[b]thiophene as a solid: 1H NMR (600 MHz, DMF- d_7) 8.11 (m, 1H), 7.94 (m, 1H), 7.89 (d, J = 8.7, 1H), 7.61 (dq, J = 9.9, 1H), 7.51 (m, 3H), 7.20 (s, 1H), 7.12 (m, 1H), 7.12 (d, J = 8.4, 1H), 6.75 (d, J = 1.5, 1H), 5.72 (s, 1H), 2.36 (d, J = 1.2, 3H), 1.48 (s, 3H), 1.45 (s, 3H).

EXAMPLE 53

Preparation of (-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline and (+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 64 and 65, Structure 7 of Scheme II, where R⁸ = 2-benzo[b]thiophene).

Compounds 64 and 65 were prepared by chiral HPLC separation of Compound 63 (Structure 7 of Scheme II, where R⁸ = 2-benzothiophene) as pure enantiomers. Retention times: (R,R) Whelk-O2 10/100; 0.46 cm x 25 cm, flow 1ml/min, heptanes/isopropanol 98/2; Rt = 14 min and 18 min. Compound 64 is the (-)-isomer; and compound 10 65 is the (+)-isomer.

EXAMPLE 54

Preparation of (±)-7,9-difluoro-5-(5-methyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 66, Structure 7 of Scheme II, where R⁸ = 5-methyl-2-furyl).

15 Compound 66 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 5-methyl-2-(tributylstannyl)furan as a solid: ¹H NMR (400 MHz, DMF-*d*₇) 7.82 (m, 1H), 7.62 (m, 1H), 7.12 (m, 2H), 7.05 (m, 1H), 6.65 (s, 1H), 6.07 (s, 1H), 5.92 (m, 1H), 5.67 (s, 1H), 2.41 (dd, *J* = 8.4, 3H), 2.22 (d, *J* = 8, 3H), 1.44 (m, 3H), 1.39 (m, 3H).

EXAMPLE 55

Preparation of (\pm)-7,9-difluoro-5-(2-benzo[b]furyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 67, Structure 7 of Scheme II, where R⁸ = 2-benzo[b]furyl).

5 Compound 67 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-(tributylstannyl)benzo[b]furan as a solid: ¹H NMR (400 MHz, CDCl₃) 7.49 (d, *J* = 8.6, 1H), 7.40 (d, *J* = 8.6, 1H), 7.36 (d, *J* = 8.4, 1H), 7.26 (m, 1H), 7.14 (m, 1H), 7.08 (m, 2H), 6.71 (d, *J* = 8.4, 1H), 6.58 (m, 1H), 6.23 (s, 1H), 5.48 (d, *J* = 1.4, 1H), 4.05 (s, 1H), 2.04 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H).

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EXAMPLE 56

Preparation of (\pm)-7,9-difluoro-5-[4-(dimethylamino)phenyl]-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 68, Structure 7 of Scheme II, where R⁸ = 4-dimethylaminophenyl).

15 Compound 68 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and (3-[dimethylamino]phenyl)tributyltin as a solid: ¹H NMR (400 MHz, DMSO-*d*₆) 7.54 (d, *J* = 8.8, 1H), 7.32 (dq, *J* = 10.2, 1H), 6.92 (m, 2H), 6.88 (m, 1H), 6.85 (s, 1H), 6.74 (d, *J* = 8.6, 1H), 6.54 (m, 2H), 6.43 (d, *J* = 1.8, 1H), 5.38 (s, 1H), 2.82 (s, 6H), 1.90 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H).

EXAMPLE 57

Preparation of (\pm)-7,9-difluoro-5-(5-methyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 69, Structure 7 of Scheme II, where R^8 = 5-methyl-2-thiophene).

5 Compound 69 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 5-methyl-2-(tributylstannylyl)thiophene as a solid: 1H NMR (400 MHz, DMSO- d_6) 7.55 (d, J = 8.6, 1H), 7.36 (dq, J = 10.2, 1.8, 1H), 7.05 (s, 1H), 6.96 (m, 1H), 6.75 (d, J = 3.4, 1H), 6.52 (dd, J = 3.8, 1.2, 1H), 6.48 (d, J = 2, 1H), 6.40 (d, J = 3.4, 1H), 5.41 (s, 1H), 2.11 (s, 3H), 2.01 (s, 3H), 1.18 (s, 3H),
10 1.17 (s, 3H).

EXAMPLE 58

Preparation of (\pm)-7,9-difluoro-5-(5-methoxy-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 70, Structure 7 of Scheme II, where R^8 = 5-methoxy-2-furyl).

15 Compound 70 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 5-methoxy-2-(tributylstannylyl)furan as a solid: 1H NMR (600 MHz, CDCl₃) 7.35 (d, J = 8.7, 1H), 7.06 (dt, J = 9.6, 1H), 6.80 (s, 1H), 6.65 (d, J = 8.4, 1H), 6.62 (m, 1H), 5.69 (d, J = 3.3, 1H), 5.47 (s, 1H), 4.88 (d, J = 3.3, 1H), 3.98 (s, 1H), 3.79 (s, 3H), 2.05 (d, J = 0.9, 3H), 1.29 (s, 3H), 1.22 (s, 3H).

EXAMPLE 59

Preparation of (\pm)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 71, Structure 7 of Scheme II, where $R^8 = 2$ -propynyl).

5 Compound 71 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-propynyltributyltin as a solid: 1H NMR (400 MHz, DMF-*d*₇) 7.57 (d, *J* = 8.8, 1H), 7.43 (dq, *J* = 10.4, 1.8, 1H), 7.05 (m, 1H), 6.77 (d, *J* = 8.6, 1H), 6.44 (s, 1H), 6.19 (q, *J* = 4.6, 1H), 5.51 (t, *J* = 1.8, 1H), 2.84 (t, *J* = 2.8, 1H), 2.64 (m, 1H), 2.48 (dq, *J* = 17.6, 2.8, 1H), 2.27 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H).

EXAMPLE 60

Preparation of (-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline and (+)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compounds 72 and 73, Structure 7 of Scheme II, where $R^8 = 2$ -propynyl).

Compounds 72 and 73 were prepared by chiral HPLC separation of Compound 71 (Structure 7 of Scheme II, where $R^8 = 2$ -propynyl) as pure enantiomers. Retention times: OJ column 2.0 cm x 50 cm, flow 10 ml/min, heptanes/ethanol 90/10; *Rt* = 40 min and 45 min. Compound 72 is the (-)-isomer; and Compound 73 is the (+)-isomer.

EXAMPLE 61

Preparation of (\pm)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 74, Structure 7 of Scheme II, where R^8 = 1-propynyl).

5 Compound 74 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and (1-propynyl)tributyltin as a solid: 1H NMR (400 MHz, DMSO- d_6) 7.46 (d, J = 8.6, 1H), 7.42 (dq, J = 10,1.8, 1H), 7.08 (m, 1H), 6.67 (d, J = 8.6, 1H), 6.54 (q, J = 2.2, 1H), 6.48 (d, J = 2, 1H), 5.46 (t, J = 1.6, 1H), 2.29 (s, 3H), 1.69 (d, J = 2, 3H), 1.25 (s, 3H), 1.11 (s, 3H).

10 **EXAMPLE 62**

Preparation of (-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline and (+)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compounds 75 and 76, Structure 7 of Scheme II, where R^8 = 1-propynyl).

15 Compounds 75 and 76 were prepared by chiral HPLC separation of Compound 74 (Structure 7 of Scheme II, where R^8 = 1-propynyl) as pure enantiomers. Retention times: OJ column 2.0 cm x 50 cm, flow 10 ml/min, heptanes/ethanol 90/10; Rt = 37 min and 47 min. Compound 75 is the (-)-isomer; and Compound 76 is the (+)-isomer.

EXAMPLE 63

Preparation of (\pm)-7,9-difluoro-5-(4,5-dimethyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 77, Structure 7 of Scheme II, where R^8 = 4,5-dimethyl-2-furyl).

5 Compound 77 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2,3-dimethyl-5-(tributylstannyl)furan as a solid: 1H NMR (400 MHz, DMSO- d_6) 7.54 (d, J = 8.6, 1H), 7.39 (dq, J = 10, 1.8, 1H), 6.97 (m, 1H), 6.80 (s, 1H), 6.74 (d, J = 8.4, 1H), 6.46 (d, J = 1.8, 1H), 5.55 (s, 1H), 5.40 (s, 1H), 2.12 (s, 3H), 1.92 (s, 3H), 1.69 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H).

10 **EXAMPLE 64**

Preparation of (\pm)-7,9-difluoro-5-(2-methyl-1-propenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 78, Structure 7 of Scheme II, where R^8 = 2-methyl-1-propenyl).

15 Compound 78 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 2-methylpropenylmagnesium bromide as a solid: 1H NMR (400 MHz, DMSO- d_6) 7.47 (d, J = 8.6, 1H), 7.36 (m, 1H), 6.98 (m, 1H), 6.66 (d, J = 8.4, 1H), 6.41 (d, J = 1.8, 1H), 6.38 (d, J = 7.4, 1H), 5.42 (s, 1H), 5.17 (d, J = 7.6, 1H), 2.11 (s, 3H), 1.88 (s, 3H), 1.62 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H).

EXAMPLE 65

Preparation of (\pm)-7,9-difluoro-5-(3,4-dimethyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 79, Structure 7 of Scheme II, where R^8 = 3,4-dimethyl-2-thiophene).

5 Compound 79 was prepared in a similar fashion as that described in Example 34 from Compound 32 (Structure 6 of Scheme II) and 3,4-dimethyl-2-(tributylstannyli)thiophene as a solid: 1H NMR (600 MHz, DMSO- d_6) 7.55 (d, J = 9, 1H), 7.38 (m, 1H), 7.12 (s, 1H), 6.91 (m, 1H), 6.87 (s, 1H), 6.76 (d, J = 8.4, 1H), 6.46 (d, J = 1.8, 1H), 5.38 (s, 1H), 2.27 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H).

10 **EXAMPLE 66**

Preparation of (\pm)-7,9-difluoro-5-(3-(3-bromophenyl)phenyl)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 80, Structure 7 of Scheme II, where R^8 = 3-(3-bromophenyl)phenyl).

15 Compound 80 was isolated as a minor product of the reaction described in example 31 as a solid: 1H NMR (600 MHz, DMSO- d_6) 7.65 (t, J = 2.1, 1H), 7.58 (d, J = 8.7, 1H), 7.55 (m, 1H), 7.49 (m, 1H), 7.41 (t, J = 8.4, 1H), 7.35 (m, 2H), 7.09 (d, J = 7.8, 1H), 7.08 (s, 1H), 6.93 (m, 1H), 6.79 (d, J = 8.7, 1H), 6.53 (d, J = 2.1, 1H), 5.45 (s, 1H), 1.97 (s, 3H), 1.21 (s, 6H).

EXAMPLE 67

Preparation of 7,9-difluoro-5(Z)-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 81, Structure 2 of Scheme I, where R⁹ = 2-methylphenyl).

5 This compound was prepared in a similar fashion as that described in Example 1 from 2-methylbenzyl Grignard reagent and Compound 11 (Structure 1 of Scheme I) as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) 8.30 (d, J = 8.0, 1H), 7.38 (d, J = 8.4, 1H), 7.31-7.24 (m, 1H), 7.17-7.10 (m, 4H), 6.73-6.82 (m, 1H), 6.66 (d, J = 8.4, 1H), 5.96 (s, 1H), 5.53 (s, 1H), 4.24 (s, 1H), 2.28 (s, 3H), 2.14 (s, 3H), and 1.25 (bs, 6H).

10

EXAMPLE 68

The PR modulating activities and binding affinities of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and the standard receptor competitive binding assays, according to the following illustrative Examples. The receptor-selectivities of the selected analogues 15 towards PR relative to other steroid hormone receptors were also assessed in the cotransfection assay under the same cell background. The potential tissue-selectivities of the selected analogues were examined by using the T47D alkaline phosphatase assay that was developed from human breast cancer cells with endogenous PRs.

Cotransfection assay

20 The function and detailed preparation procedure of the cotransfection assays have been described previously (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga Cymoplia Barbata. *Mol. Pharm.* 1995, 47, 630-635). Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard

calcium phosphate coprecipitation procedure (Berger, T. S. *et al.*, Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor. *J. Steroid Biochem. Mol. Bio.* 1992, 41, 733-738) with the Plasmid containing receptor, MTV-LUC reporter, pRS- β -Gal, and filler DNA (Rous sarcoma virus chloramphenicol acetyltransferase).

5 The agonist activity was determined by examining the LUC expression (normalized response) and the efficacy readout was a relative value to the maximal LUC expression produced by a reference agonist as 100%, *e.g.*, progesterone for hPR, dihydrotestosterone (DHT) for human androgen receptor (hAR), dexamethasone for hGR, aldosterone for human mineralocorticoid receptor (hMR) and estradiol for human 10 estrogen receptor (hER). Antagonist efficacy was determined as a function (%) of maximal inhibition of a reference agonist at EC₅₀ concentration. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

Receptor Binding Assays

15 The preparation of receptor binding assays for hPR-A was described in literature (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marie Alga Cymopolia Barbata. *Mol. Pharm.* 1995, 47, 630-635.)

T47D Alkaline Phosphatase Assay

The T47D alkaline phosphatase assays were performed as described previously 20 (Lorenzo, D. D. *et. Al.*, Progestin Regulation of Alkaline phosphatase in the Human Breast Cancer Cell Line T47D. *Cancer Res.* 1991, 51, 4470).

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR are shown in Table 1 below. Efficacy is reported as the percent

maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Table 1 for each compound is its antagonist potency or IC₅₀ (which is the concentration (nM), required to reduce the maximal response by 50%), and its agonist potency or EC₅₀ (nM), *which is the effective concentration that produced 50% of the maximum response*. Table 1 also lists the PR modulating activity in T47D cells to assess the potential tissue-selectivity comparing to marketed steroidal progestins or antiprogestins. All of the reference steroids demonstrated full agonist or antagonist activities in both cell lines; however, the 7,9-difluoro compounds of the subject invention behaved as partial agonist/antagonist activities in human breast cancer cell line despite the full agonist or antagonist activities in the CV-1 cells.

Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compounds and reference antagonists compounds.

Cmpd	hPR Agonist CV-1 Cells		hPR Antagonist CV-1 Cells		hPR AgonistT47D cells		hPR Antagonists T47D Cells		PR bind ing
	Eff. (%)	EC ₅₀ (nM)	Eff. (%)	IC ₅₀ (nM)	Eff. (%)	EC ₅₀ (nM)	Eff. (%)	IC ₅₀ (nM)	
Prog.	100	0.5	na	na	100	2.3	na	na	3.5
MPA	88	0.4	na	na	114	0.7	na	na	1.4
Norethindrone	170	1.2	na	na	103	0.7	na	na	1.2
Levonorgestrel	216	0.1	na	na	96	0.5	na	na	0.4
Drospirenone	87	2.2	na	na	117	6.0	na	na	12
3-ketodesogestrel	190	0.1	na	na	94	0.2	na	na	0.3
RU486	na	na	94	0.6	na	na	94	3.7	1.1
ZK299	na	na	99	1.6	na	na	86	2.8	18
10	153	4.9	na	na	54	30	49	97	6.8
14	103	7.4	na	na	58	49	44	116	6.0
15	191	3.8	na	na	56	19	52	711	9.7
17	169	2.9	na	na	62	12	42	389	9.5
18	142	1.3	na	na	57	17	58	55	3.9
19	212	1.4	na	na	65	8.7	35	360	8.5
20	147	2.8	na	na	63	6.6	59	170	2.9
24	52	9.4	na	na	72	79	26	830	58
26	159	0.6	na	na	63	7.5	46	610	9.0
29	191	2.3	na	na	62	8.7	40	170	7.0
30	186	5.3	na	na	66	33	44	840	4.5
31	171	2.7	na	na	66	14	39	610	7.9
32	na	na	76	75	36	315	35	250	37
33	85	3.5	na	na	62	35	na	na	2.7
34	114	1.2	na	na	60	34	47	565	2.5
37	89	1.24	na	na	50	130	56	150	2.2
38	110	1.2	na	na	54	6.2	nt	nt	2.0
39	26	28	62	24	na	na	29	4100	nt
41	146	1.87	na	na	54	42	50	135	2.8
45	na	na	79	42	77	195	na	na	18
63	154	2.3	na	na	61	20	49	490	6.5
74	89	0.7	na	na	58	4.6	40	53	3.5

5

na = not active (i.e. efficacy of <20 and potency of >10,000)

nt = not tested

The receptor-selectivity profile of selected analogues was examined in the cotransfection assays with different steroid hormone receptors in comparison with the steroid reference compounds and Table 2 lists the receptor-selectivity potency ratio of selected 7,9-difluoro analogues and PR modulating steroids. In general, the nonsteroidal analogues demonstrated more selectivity towards hPR than the steroids.

Table 2: Progesterone receptor-selectivity of selective PR modulator compounds of present invention and the reference steroidal progestins.

Cmpd	hAR EC ₅₀ or IC ₅₀ / hPR EC ₅₀	hGR EC ₅₀ or IC ₅₀ / hPR EC ₅₀	hMR EC ₅₀ or IC ₅₀ / hPR EC ₅₀	hER EC ₅₀ or IC ₅₀ / hPR EC ₅₀
Prog	23	>1000	25	>1000
MPA	41	67	>1000	>1000
Noret hindro ne	33	34	>1000	9
Levonor gestrel	>1000	142	>1000	>1000
3- ketodeso gestrel	>1000	896	>1000	>1000
10	320	290	>1000	>1000
14	54	365	>1000	>1000
15	2	30	>1000	>1000
17	622	66	>1000	>1000
18	170	77	>1000	>1000
19	>1000	432	>1000	>1000
20	8	27	>1000	>1000
26	742	342	>1000	>1000
29	6	83	>1000	>1000
30	377	19	>1000	>1000
31	517	59	>1000	>1000
33	37	10	>1000	>1000
34	8.5	>1000	>1000	>1000
37	558	54	>1000	>1000
41	252	105	905	>1000
63	136	8.8	>1000	685
74	100	>1000	>1000	>1000

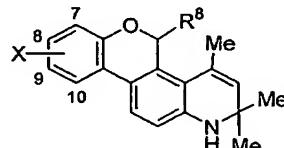
EXAMPLE 69

The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in modulating PR activities, which is unexpected and surprising, in view of US Patents No. 5,693,646 and 5,696,127.

5 The superiority of the 7,9-difluoro analogue compounds of the present invention was demonstrated utilizing the hPR cotransfection assay according to the following illustrative Examples. The EC₅₀ comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (disclosed in US Patents No. 5,693,646 and 5,696,127) are tabulated in Tables 3 and 4.

10

Table 3: hPR agonist potencies (EC₅₀ in nM) of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in the cotransfection assay.



5

X →	7,9-diF		H	9-F	9-OMe	9-Cl	9-Me	8-F
R ⁸	#	EC ₅₀						
Ph	33	3.5	203 ^a	7.4 ^b	- ^c	6.9 ^b	-	-
3-F-Ph	40	6.66	9 ^a	-	-	3.7 ^b	-	-
3-Cl-Ph	41	1.87	18 ^b	2.8 ^b	-	3.6 ^b	4.85	-
4-Cl-Ph	43	5.1	15 ^b	8.1 ^b	3.1 ^b	9 ^b	-	10 ^b
3-Br-Ph	42	3.65	8 ^b	-	-	-	-	-
4-Br-Ph	36	4.96	14 ^b	-	-	5.2 ^b	-	-
3-Me-Ph	34	1.2	145	5.0 ^b	11	7.1 ^b	44	-
3-CF ₃ -Ph	56	1.6	13 ^a	10 ^b	-	7.4	-	-
4-Cl-3-Me-Ph	37	1.24	14 ^b	2.7 ^b	-	9.4	7.45	-
Benzodioxol-5-yl	35	3.85	48	-	-	-	-	-
Me	44	1.4	2067	13	-	3	-	-
Et	46	6.93	-	9	-	-	-	-
Allyl	55	3.6	839	7.5	-	-	-	-
Bu	52	15	16 ^a	16 ^a	9	7	16	5285

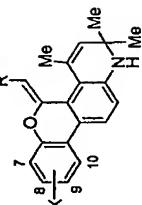
^a EC₅₀ data from US Pats 5693646/5693647/5696127;

^b EC₅₀ data from *J. Med. Chem.* 41 (1998), 291 and 303;

^c “-” means compound not prepared.

10

Table 4: hPR agonist potencies (EC₅₀ in nM) of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in the cotransfection assay.



X →		7,9-difF	H	9-F	8-OH	9-OH	8-OMe	9-OMe	7-Cl	9-Cl	9-Me	8-F	8,9-difF
R ⁹	#	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀
Phenyl	10	4.9	33 ^a	5.25	- ^c	54.4	5.5	67	6.2	6.24	-	187	-
2-F-Ph	12	2.55	29 ^b	7.3	-	45	-	-	26.5	-	-	-	-
3-F-Ph	15	3.8	7.6 ^b	7	-	5.75	8.6	-	-	11.6	7.95	109	-
4-F-Ph	16	3.7	59.5 ^b	3.95	-	-	-	-	-	-	-	-	-
2-Cl-Ph	13	1.92	57.8 ^b	12	-	>1000	-	-	-	-	-	-	-
2,5-difF-Ph	17	2.9	14.7 ^b	3	10	10	-	-	25	-	-	-	-
2-Me-3-F-Ph	21	8.2	-	8.4	-	-	-	-	-	-	-	-	-
2-Me-5-F-Ph	19	1.4	2.6	2.1	-	-	-	-	-	2.1	-	-	3.95
2-MeO-5-F-Ph	26	0.6	-	0.9	-	11.5	-	-	-	-	-	-	-
2-MeO-Ph	18	1.3	-	0.93	-	-	24.0	-	-	-	-	-	-
2-Me-Ph	81	1.66	5.7 ^b	4 ^b	-	9.3	3.5	67.5	-	8.5	-	13	13
4-pyridinyl	14	7.4	-	5.8	-	-	36	-	-	-	-	-	-
3-Me-4-pyridinyl	20	2.8	-	2.0	-	-	24	-	-	-	-	-	-
2-Thienyl	31	2.7	-	18	-	-	-	-	-	-	-	-	-

^a EC₅₀ data from US Pats 5693646/5693647/5696127;

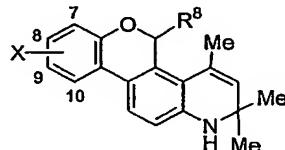
^b EC₅₀ data from *J. Med. Chem.*, 41 (1998), 291 and 303;

^c “-” means compound not prepared.

EXAMPLE 70

The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in tissue-selectivity, which is unexpected and surprising, in view of US Patents No. 5,693,646 and 5,696,127. The 5 superiority of the 7,9-difluoro analogue compounds of the present invention was further characterized utilizing a multi-endpoint adult rat model according to the following illustrative Examples. In this assay, advantage is taken of the fact that in the uterus, estrogens induce a proliferation and increase in the epithelial cell height and uterine wet weight, which can be antagonized by progestins. In the breast, estrogens induce a 10 proliferation of the ductal network while progestins stimulate the growth of the lobular-alveolar end buds, which grow from the distal end of the ducts. The assay is carried out in ovariectomized female rats by treating them for three days with estrone or estrone plus varying doses of a progestin; in this case MPA was used. Proliferating cells or inhibition of proliferating cells were quantitated either by measurements of cell height in sectioned 15 and stained tissue samples or, in the case of the breast, immuno-histochemically labeled Brdu incorporated nuclei. The tissue-selectivity comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (disclosed in US Patents No. 5,693,646 and 5,696,127) are tabulated in Tables 5 and 6. The uterus/breast tissue-selectivity is presented as the ratio of relative efficacy to MPA in 20 uterus verse in breast tissue at the same highest dose tested.

Table 5: The uterus/breast tissue-selectivity of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in an adult rat model.

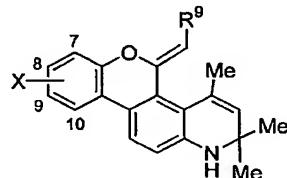


5

X →	7,9-difF		H	9-F
	R ⁸	Compd #		
Ph	33	- ^a	0.78	-
n-butyl	52	-	-	2.0
2-benzo-thiophene	64	2.8	-	-
4-Cl-3-Me-Ph	38	2.8	-	-
1-propynyl	75	4.2	-	-
4-Cl-Ph	43	-	1.5	-
3-CF ₃ -Ph	56	-	3.5	-

^a “-” means compound not tested in the assay.

Table 6: The uterus/breast tissue-selectivity of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in an adult rat model.



10

X →	7,9-difF		H	9-F
	R ⁸	Compd #		
2,5-diF-Ph	17	2.7	- ^a	-
3-F-Ph	15	-	0.69	2.2
2-thienyl	31	3.5	-	-
2-Me-5-F-Ph	19	3.5	-	-
2-Me-Ph	81	-	-	2.3

15

^a “-” means compound not tested in the assay.

EXAMPLE 71

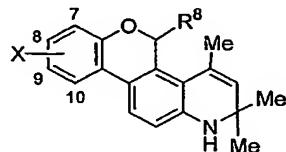
The 7,9-difluoro substituents at the D-ring of formulae I and II of the present invention are generally superior to any other substituents in PR agonist activity *in vivo*, which is unexpected and surprising, in view of US Patents No. 5,693,646 and 5,696,127.

5 The superiority of the 7,9-difluoro analogue compounds of the present invention was further characterized utilizing the McPhail rabbit model according to the following illustrative Examples. The Clauberg or McPhail assay is a classic assay utilizing rabbits to measure progestational activity. The reason rabbit is used is because the results observed in rabbit have proved to be a good indicator and predictor of activity in the

10 human. In this assay, immature rabbits are treated initially with estradiol, which induces growth in the uterus. This is followed by a progestin, which causes a large change in the glandular content of the uterus. It is this change in the glandular component which is a measure of the progestational activity of a progestin. The measurement of these glandular changes is carried out histologically using stained sections of the uterus. The *in*

15 *vivo* comparison between the new 7,9-difluoro compounds and analogues with substitution patterns different from 7,9-difluoro (US Patent No. 5,693,646 and 5,696,127) is tabulated in Tables 7 and 8. The *in vivo* potency of the progestins is presented as the minimum active dose (MAD).

Table 7: The potency (MAD in mg/kg) of selected 7,9-difluoro compounds of present invention (Formula I) and analogues with other D-ring substitution patterns in the McPhail assay.

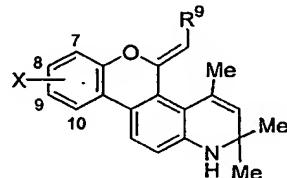


5

X →	7,9-diF		7-F	9-F	9-Me
R⁸	Compd #	MAD	MAD	MAD	MAD
3-F-Ph	40	- ^a	-	-	>2
3-Me-Ph	34	1.0	-	-	-
2-benzo-thiophene	64	0.25	-	-	-
4-Cl-3-Me-Ph	38	0.25	0.5	1.0	-
1-propynyl	75	<0.5	-	-	-
2-propynyl	71	<0.5	-	-	-
3-Cl-Ph	41	0.75	-	-	-

^a “-” means compound not tested in the assay.

Table 8: The potency (MAD in mg/kg) of selected 7,9-difluoro compounds of present invention (Formula II) and analogues with other D-ring substitution patterns in the McPhail assay.



5

X →	7,9-diF		7-F	9-F	
	R ⁸	Compd #	MAD	MAD	
2,5-diF-Ph		17	0.25	0.5	- ^a
2-F-Ph		12	0.5	-	-
3-F-Ph		15	0.18	-	-
2-MeO-Ph		18	2.0	-	-
2-Me-5-F-Ph		19	0.1	1.0	-
2-MeO-5-F-Ph		26	2.0	-	-
2-Me-Ph		81	-	-	1.2
3-Me-pyridine-4-		20	0.25	-	-

^a “-” means compound not tested in the assay.

Pharmacological and Other Applications

The following Example provides illustrative pharmaceutical composition

10 formulations:

EXAMPLE 72

Hard gelatin capsules are prepared using the following ingredients:

	<u>Quantity</u> (<u>mg/capsule</u>)
COMPOUND 10	10
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	220 mg

The above ingredients are mixed and filled into hard gelatin capsules in 220 mg

5 quantities.

A tablet is prepared using the ingredients below:

	<u>Quantity</u> (<u>mg/tablet</u>)
COMPOUND 10	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	<u>10</u>
Total	230 mg

The components are blended and compressed to form tablets each weighing 230 mg.

Tablets, each containing 10 mg of active ingredient, are made as follows:

	<u>Quantity</u> (<u>mg/tablet</u>)
COMPOUND 10	10
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	<u>1.0</u>
Total	100 mg

10

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are

dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

5 Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	<u>Quantity</u> (mg/suppository)
COMPOUND 10	20
Saturated fatty acid glycerides	<u>2,000</u>
Total	2,020 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

	<u>Quantity</u>
COMPOUND 10	10 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

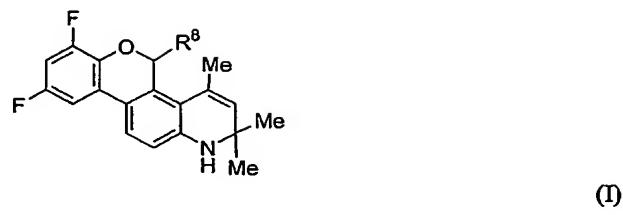
The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised 5 material is specifically recited herein.

The scope of the invention is not limited by the description of the examples. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined 10 by the appended claims, rather than by the specific examples which have been presented by way of example.

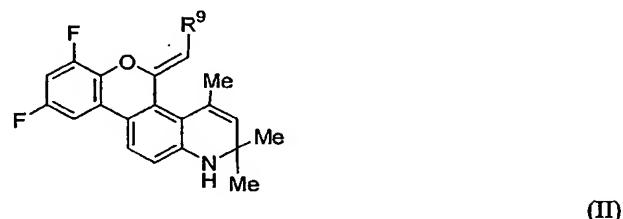
What is claimed is:

1. A compound of the formula:



5

or



wherein:

R^8 is selected from the group of C_1-C_{12} alkyl, C_1-C_{12} heteroalkyl, C_1-C_{12}

10 haloalkyl, C_2-C_{12} alkenyl, C_2-C_{12} heteroalkenyl, C_2-C_{12} haloalkenyl, C_2-C_{12} alkynyl, C_2-C_{12} heteroalkynyl, C_2-C_{12} haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1-C_4 alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$, SH, SCH_3 , OH, OCH_3 , OCF_3 , CF_3 , $C(O)CH_3$, CO_2CH_3 , $C(O)NH_2$, OR^{10} , SR^{10} , and $NR^{10}R^{11}$;

15 R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkenyl or cycloalkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 haloalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_2-C_8 haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1-C_4 alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$,

SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

R¹⁰ and R¹¹ each independently is hydrogen, or C₁—C₄ alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

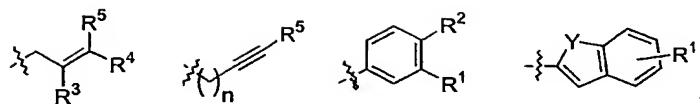
5 2. A compound according to claim 1, wherein R⁸ is selected from the group of C₁—C₈ alkyl, C₁—C₈ heteroalkyl, C₁—C₈ haloalkyl, C₂—C₈ alkenyl, C₂—C₈ heteroalkenyl, C₂—C₈ haloalkenyl, C₂—C₈ alkynyl, C₂—C₈ heteroalkynyl, C₂—C₈ haloalkynyl, aryl and heteroaryl, optionally substituted with one or more substituents independently selected from the group of hydrogen, C₁—C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂,

10 SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

3. A compound according to claim 2, wherein R⁸ is selected from the group of C₁—C₄ alkyl, C₁—C₄ heteroalkyl, C₁—C₄ haloalkyl, C₂—C₄ alkenyl, C₂—C₄ heteroalkenyl, C₂—C₄ haloalkenyl, C₂—C₄ alkynyl, C₂—C₄ heteroalkynyl, and C₂—C₄ haloalkynyl.

15 4. A compound according to claim 2, wherein R⁸ is selected from the group of aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from the group of hydrogen, C₁—C₄ alkyl, F, Cl, Br, CN, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

20 5. A compound according to claim 2, wherein R⁸ is selected from the group of



R^1 and R^2 each independently is selected from the group of hydrogen, F, Cl, Br and C_1 – C_4 alkyl;

R^3 through R^5 each independently is selected from group of hydrogen, F, Cl, and
5 C_1 – C_4 alkyl;

n is 0 or 1; and

Y is selected from the group of O, S, and NR^{10} .

6. A compound according to claim 1, wherein R^9 is selected from the group of hydrogen, F, Cl, Br, CN, C_1 – C_6 alkyl, C_1 – C_6 heteroalkyl, C_1 – C_6 haloalkyl, C_2 – C_6 alkenyl or cycloalkenyl, C_2 – C_6 heteroalkenyl, C_2 – C_6 haloalkenyl, C_2 – C_6 alkynyl, C_2 – C_6 heteroalkynyl, C_2 – C_6 haloalkynyl, aryl and heteroaryl optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1 – C_4 alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$, SH, SCH_3 , OH, OCH_3 , OCF_3 , CF_3 , $C(O)CH_3$, CO_2CH_3 , $C(O)NH_2$, OR^{10} , SR^{10} , and $NR^{10}R^{11}$.

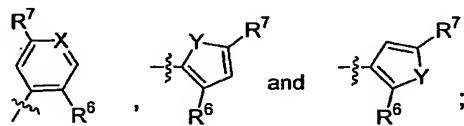
15 7. A compound according to claim 6, wherein R^9 is selected from the group of hydrogen, Br, Cl, C_1 – C_4 alkyl, C_1 – C_4 heteroalkyl, C_1 – C_4 haloalkyl, C_2 – C_4 alkenyl, C_2 – C_4 heteroalkenyl, C_2 – C_4 haloalkenyl, C_2 – C_4 alkynyl and C_2 – C_4 heteroalkynyl, C_2 – C_4 haloalkynyl.

8. A compound according to claim 6, wherein R^9 is selected from the group of aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1 – C_4

alkyl, F, Cl, Br, CN, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

9. A compound according to claim 6, wherein R⁹ is selected from the group of

5



R⁶ is selected from the group of hydrogen, F, Cl, Br, C₁–C₄ alkyl, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

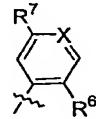
R⁷ is hydrogen, F, or Cl;

R¹⁰ and R¹¹ each independently is hydrogen, or C₁–C₄ alkyl;

10 X is CH or N; and

Y is selected from the group of O, S, and NR¹⁰.

10. A compound according to claim 9, wherein R⁹ is



15 R⁶ is selected from the group of hydrogen, F, Cl, C₁–C₄ alkyl, OMe, OEt, NHMe, and NMe₂;

R⁷ is hydrogen, F, or Cl; and

X is CH or N.

11. A compound according to claim 9, where R⁶ is selected from the group of F, Me, Et, OMe, OEt, SMe, and NMe₂.

12. A compound according to claim 1, wherein said compound is selected 5 from the group of:

7,9-difluoro-5(Z)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 10);

7,9-difluoro-5(Z)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 12);

10 7,9-difluoro-5(Z)-(2-chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 13);

7,9-difluoro-5(Z)-(4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 14);

15 7,9-difluoro-5(Z)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 15);

7,9-difluoro-5(Z)-(4-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 16);

7,9-difluoro-5(Z)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 17);

20 7,9-difluoro-5(Z)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5H-chromeno[3,4-f]quinoline (Compound 18);

7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 19);

7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 20);

5 7,9-difluoro-5(*Z*)-(2-methyl-3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 21);

7,9-difluoro-5(*Z*)-(3-methyl-2-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 22);

10 7,9-difluoro-5(*Z*)-(2,3-dimethylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 23);

7,9-difluoro-5(*Z*)-cyanomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 24);

7,9-difluoro-5(*Z*)-hexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 25);

15 7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 26);

7,9-difluoro-5(*Z*)-(2,4,5-trifluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 27);

20 7,9-difluoro-5-methylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 28);

7,9-difluoro-5(*Z*)-bromomethylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 29);

7,9-difluoro-5(*Z*)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 30);

5 7,9-difluoro-5(*Z*)-(2-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 31);

(\pm)-7,9-difluoro-5-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 32);

10 (\pm)-7,9-difluoro-5-phenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 33);

(\pm)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 34);

(\pm)-7,9-difluoro-5-(1,3-benzodioxol-5-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 35);

15 (\pm)-7,9-difluoro-5-(4-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 36);

(\pm)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 37);

20 (-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 38);

(+)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 39);

(\pm)-7,9-difluoro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 40);

5 (\pm)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 41);

(\pm)-7,9-difluoro-5-(3-bromophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 42);

10 (\pm)-7,9-difluoro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 43);

(\pm)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 44);

(\pm)-7,9-difluoro-5-(2-oxo-2-phenylethyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 45);

15 (\pm)-7,9-difluoro-5-ethyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 46);

(\pm)-7,9-difluoro-5-ethenyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 47);

20 (\pm)-7,9-difluoro-5-(2-oxo-3-butenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 48);

(\pm)-7,9-difluoro-1,2-dihydro- $\alpha,\alpha,2,2,4$ -pentamethyl-5*H*-chromeno[3,4-*f*]quinoline-5-ethanoate (Compound 49);

(\pm)-7,9-difluoro-5-ethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 50);

5 (\pm)-7,9-difluoro-5-cyano-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 51);

(\pm)-7,9-difluoro-5-butyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 52);

10 (\pm)-7,9-difluoro-5-(2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 53);

(\pm)-7,9-difluoro-5-(2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 54);

(\pm)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 55);

15 (\pm)-7,9-difluoro-5-[3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 56);

Ethyl (\pm)-7,9-difluoro-1,2-dihydro- α -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanoate (Compound 57);

20 (\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol (Compound 58);

(\pm)-7,9-difluoro-1,2-dihydro- β -methylene-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline-5-propanol acetate(Compound 59);

(\pm)-7,9-difluoro-5-(1-methylethenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 60);

5 (\pm)-7,9-difluoro-5-(N-methyl-2-pyrrolyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 61);

(\pm)-7,9-difluoro-5-phenylethynyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 62);

10 (\pm)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 63);

(-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 64);

(+)-7,9-difluoro-5-(benzo[b]thie-2yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 65);

15 (\pm)-7,9-difluoro-5-(5-methyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 66);

(\pm)-7,9-difluoro-5-(2-benzo[b]furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 67);

20 (\pm)-7,9-difluoro-5-[4-(dimethylamino)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 68);

(\pm)-7,9-difluoro-5-(5-methyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 69);

(\pm)-7,9-difluoro-5-(5-methoxy-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 70);

5 (\pm)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 71);

(-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 72);

10 (+)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 73);

(\pm)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 74);

(-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 75);

15 (+)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 76);

(\pm)-7,9-difluoro-5-(4,5-dimethyl-2-furyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 77);

20 (\pm)-7,9-difluoro-5-(2-methyl-1-propenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 78);

(\pm)-7,9-difluoro-5-(3,4-dimethyl-2-thienyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 79);

(\pm)-7,9-difluoro-5-(3-(3-bromophenyl)phenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 80); and

5 7,9-difluoro-5-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 81).

13. A compound according to claim 1, wherein said compound is selected from the group of:

7,9-difluoro-5(*Z*)-benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 10);

7,9-difluoro-5(*Z*)-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 12);

7,9-difluoro-5(*Z*)-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 15);

15 7,9-difluoro-5(*Z*)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 17);

7,9-difluoro-5(*Z*)-(2-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 18);

20 7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 19);

7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 20);

7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 26);

5 7,9-difluoro-5(*Z*)-(3-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 30);

7,9-difluoro-5(*Z*)-(2-thienylmethylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 31);

10 (\pm)-7,9-difluoro-5-(3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 34);

(-)-7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 38);

(\pm)-7,9-difluoro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 41);

15 (\pm)-7,9-difluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 44);

(\pm)-7,9-difluoro-5-allyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 55);

20 (\pm)-7,9-difluoro-5-(3-trifluoromethylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 56);

(\pm)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 63);

(-)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 64);

5 (+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 65);

(-)-7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 72);

10 (-)-7,9-difluoro-5-(1-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 75); and

7,9-difluoro-5-(2-methylbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 81).

14. A compound according to claim 1, wherein said compound is selected from the group of:

15 7,9-difluoro-5(*Z*)-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 17);

7,9-difluoro-5(*Z*)-(2-methyl-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 19);

20 7,9-difluoro-5(*Z*)-(3-methyl-4-picolylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 20);

7,9-difluoro-5(*Z*)-(2-methoxy-5-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 26);

(-)7,9-difluoro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 38);

5 (±)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 63);

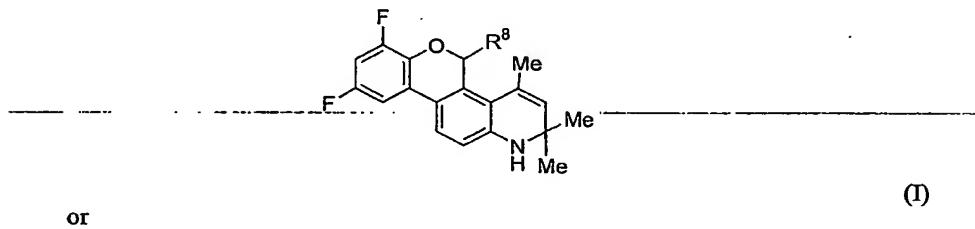
(-)7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 64);

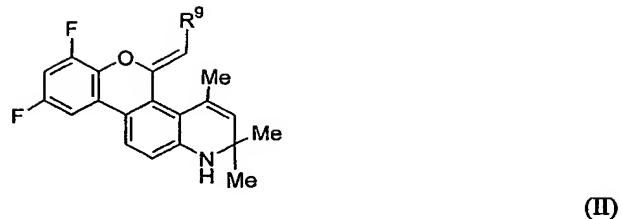
10 (+)-7,9-difluoro-5-(benzo[b]thien-2-yl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 65); and

(-)7,9-difluoro-5-(2-propynyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 72).

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:

15





wherein:

5 R^8 is selected from the group of C_1 – C_{12} alkyl, C_1 – C_{12} heteroalkyl, C_1 – C_{12} haloalkyl, C_2 – C_{12} alkenyl, C_2 – C_{12} heteroalkenyl, C_2 – C_{12} haloalkenyl, C_2 – C_{12} alkynyl, C_2 – C_{12} heteroalkynyl, C_2 – C_{12} haloalkynyl, aryl and heteroaryl optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1 – C_4 alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$, SH, SCH_3 , OH, OCH_3 , OCF_3 , CF_3 , $C(O)CH_3$, CO_2CH_3 , $C(O)NH_2$, OR^{10} , SR^{10} , and $NR^{10}R^{11}$;

10 R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1 – C_8 alkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, C_2 – C_8 alkenyl or cycloalkenyl, C_2 – C_8 heteroalkenyl, C_2 – C_8 haloalkenyl, C_2 – C_8 alkynyl, C_2 – C_8 heteroalkynyl, C_2 – C_8 haloalkynyl, aryl and heteroaryl optionally substituted with one or more substituents independently selected from the group of hydrogen, C_1 – C_4 alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$, SH, SCH_3 , OH, OCH_3 , OCF_3 , CF_3 , $C(O)CH_3$, CO_2CH_3 , $C(O)NH_2$, OR^{10} , SR^{10} , and $NR^{10}R^{11}$;

15 R^{10} and R^{11} each independently is hydrogen, or C_1 – C_4 alkyl;

— — — or a pharmaceutically acceptable salt or prodrug thereof. — — —

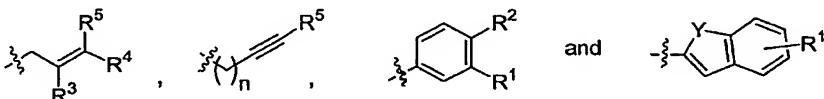
16. A pharmaceutical composition according to claim 15, wherein R^8 is selected from the group of C_1 – C_8 alkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, C_2 – C_8 alkenyl, C_2 – C_8 heteroalkenyl, C_2 – C_8 haloalkenyl, C_2 – C_8 alkynyl, C_2 – C_8 heteroalkynyl, C_2 – C_8 haloalkynyl, aryl and heteroaryl, optionally substituted with one or more

substituents independently selected from the group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

17. A pharmaceutical composition according to claim 16, wherein R⁸ is
 5 selected from the group of C₁–C₄ alkyl, C₁–C₄ heteroalkyl, C₁–C₄ haloalkyl, C₂–C₄ alkenyl, C₂–C₄ heteroalkenyl, C₂–C₄ haloalkenyl, and C₂–C₄ alkynyl, C₂–C₄ heteroalkynyl and C₂–C₄ haloalkynyl.

18. A pharmaceutical composition according to claim 16, wherein R⁸ is
 selected from the group of aryl and heteroaryl, wherein said aryl and heteroaryl groups
 10 are optionally substituted with one or more substituents independently selected from the
 group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, CN, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH,
 OCH₃, OCF₃, CF₃, C(O)CH₃, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

19. A pharmaceutical composition according to claim 16, wherein R⁸ is
 selected from the group of

15 
 R¹ and R² each independently is selected from the group of hydrogen, F, Cl, Br
 and C₁–C₄ alkyl;

R³ through R⁵ each independently is selected from the group of hydrogen, F, Cl,
 and C₁–C₄ alkyl;

20 n is 0 or 1; and

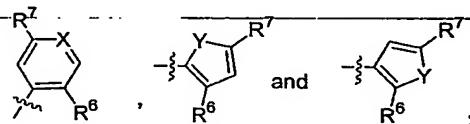
Y is selected from the group of O, S, and NR¹⁰.

20. A pharmaceutical composition according to claim 15, wherein R⁹ is selected from the group of hydrogen, F, Cl, Br, CN, C₁–C₆ alkyl, C₁–C₆ heteroalkyl, C₁–C₆ haloalkyl, C₂–C₆ alkenyl or cycloalkenyl, C₂–C₆ heteroalkenyl, C₂–C₆ haloalkenyl, C₂–C₆ alkynyl, C₂–C₆ heteroalkynyl, C₂–C₆ haloalkynyl, aryl and heteroaryl, optionally 5 substituted with one or more substituents independently selected from the group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

21. A pharmaceutical composition according to claim 20, wherein R⁹ is selected from the group of hydrogen, Br, Cl, C₁–C₄ alkyl, C₁–C₄ heteroalkyl, C₁–C₄ haloalkyl, C₂–C₄ alkenyl, C₂–C₄ heteroalkenyl, C₂–C₄ haloalkenyl, C₂–C₄ alkynyl, C₂–C₄ heteroalkynyl, and C₂–C₄ haloalkynyl.

22. A pharmaceutical composition according to claim 20, wherein R⁹ is selected from the group of aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from the 15 group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, CN, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹.

23. A pharmaceutical composition according to claim 22, wherein R⁹ is selected from the group of



20 R⁶ is selected from the group of hydrogen, F, Cl, Br, C₁–C₄ alkyl, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

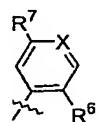
R^7 is hydrogen, F, or Cl;

R^{10} and R^{11} each independently is hydrogen, or C_1 – C_4 alkyl;

X is CH or N; and

Y is selected from group of O, S, and NR^{10} .

5 24. A pharmaceutical composition according to claim 23, wherein R^9 is



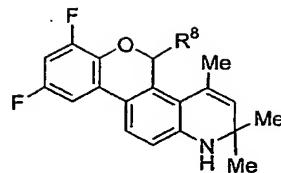
R^6 is selected from the group of hydrogen, F, Cl, C_1 – C_4 alkyl, OMe, OEt, NHMe, and NMe₂; and

R^7 is hydrogen, F, or Cl.

10 25. A pharmaceutical composition according to claim 23, where R^6 is selected from the group of F, Me, Et, OMe, OEt, SMe, and NMe₂.

26. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1 to 25.

15 27. A method according to claim 26, wherein said compound is represented by formula (I):



(I)

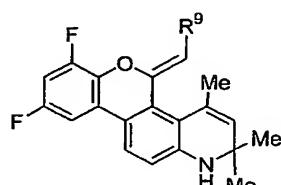
wherein:

R^8 is selected from the group of C_1-C_{12} alkyl, C_1-C_{12} heteroalkyl, C_1-C_{12}

5 haloalkyl, C_2-C_{12} alkenyl, C_2-C_{12} heteroalkenyl, C_2-C_{12} haloalkenyl, C_2-C_{12} alkynyl,
 C_2-C_{12} heteroalkynyl, C_2-C_{12} haloalkynyl, aryl and heteroaryl, optionally substituted
with one or more substituents independently selected from the group of hydrogen, C_1-C_4
alkyl, F, Cl, Br, I, CN, NO_2 , NH_2 , $NHCH_3$, $N(CH_3)_2$, SH, SCH_3 , OH, OCH_3 , OCF_3 , CF_3 ,
 $C(O)CH_3$, CO_2CH_3 , $C(O)NH_2$, OR^{10} , SR^{10} , and $NR^{10}R^{11}$;

10 or a pharmaceutically acceptable salt or prodrug thereof.

28. A method according to claim 26, wherein said compound is represented
by formula (II):



(II)

15 wherein:

R^9 is selected from the group of hydrogen, F, Cl, Br, I, CN, C_1-C_8 alkyl, C_1-C_8
heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkenyl or cycloalkenyl, C_2-C_8 heteroalkenyl, C_2-C_8
haloalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_2-C_8 haloalkynyl, aryl and
heteroaryl, optionally substituted with one or more substituents independently selected

from the group of hydrogen, C₁–C₄ alkyl, F, Cl, Br, I, CN, NO₂, NH₂, NHCH₃, N(CH₃)₂, SH, SCH₃, OH, OCH₃, OCF₃, CF₃, C(O)CH₃, CO₂CH₃, C(O)NH₂, OR¹⁰, SR¹⁰, and NR¹⁰R¹¹;

or a pharmaceutically acceptable salt or prodrug thereof.

5 29. A method according to claim 26, wherein said condition is selected from the group of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, meningiomas, hormone-dependent cancers, and female osteoporosis.

10 30. A method of modulating fertility in an individual comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1 to 25.

15 31. A method of providing contraception in an individual comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1 to 25.

32. A method according to claim 26, wherein said condition is alleviated with female hormone replacement therapy.

33. A method of modulating a progesterone receptor in an individual comprising administering a progesterone modulating effective amount of a compound according to any one of claims 1 to 25.

20 34. A method according to claim 33, wherein said modulation is activation.

35. A method according to claim 34, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a blood plasma concentration of less than 100 nM.

36. A method according to claim 34, wherein said compound provides at least 5 50% maximal activation of the progesterone receptor at a blood plasma concentration of less than 50 nM.

37. A method according to claim 34, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a blood plasma concentration of less than 20 nM.

10 38. A method according to claim 34, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a blood plasma concentration of less than 10 nM.

39. A method of treating an individual having cancer comprising administering to said individual a pharmaceutically effective amount of a compound 15 according to any one of claims 1 to 25.

40. A method of determining the presence of a progesterone receptor in a cell or cell extract comprising (a) labeling a compound according to any one of claims 1 to 25; (b) contracting the cell or cell extract with said labeled compound; and (c) testing the contracted cell or cell extract to determine the presence of progesterone receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/24420

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 A61K31/436 A61P35/00 A61P15/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 41256 A (ABBOTT LAB ;LIGAND PHARM INC (US)) 19 August 1999 (1999-08-19) cited in the application claims	1,15,26, 30,31, 33,39
P, X	ZHI, LIN ET AL: "Development of progesterone receptor antagonists from 1,2-dihydrochromeno'3,4-f!quinoline agonist pharmacophore" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2003), 13(12), 2075-2078, 16 June 2003 (2003-06-16), XP002266296 the whole document	1-40

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

*** Special categories of cited documents:**

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 January 2004

Date of mailing of the international search report

22/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Diederens, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/24420

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 26-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/24420

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9941256	A 19-08-1999	AT 230749	T	15-01-2003
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		AU 2677399	A	30-08-1999
		BG 104719	A	31-05-2001
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